NASA CONTRACTOR REPORT

NASA CR-1487

EFFECT OF SPACE ENVIRONMENT ON MAN'S RESPONSE TO INFECTION

A Review of Literature and Annotated Bibliography

by Harold V. Ellingson, Joseph F. Tomashefski, Frederick H. Shillito, and John F. Foster

Prepared by
OHIO STATE UNIVERSITY
Columbus, Ohio
for

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION • WASHINGTON, D. C. • DECEMBER 1969

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Prepared under Contract No. NSR 36-008-108
(Battelle Sub-Contract RF209-032 (No. 103)) by
OHIO STATE UNIVERSITY
Columbus, Ohio

for

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

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Springfield, Virginia 22151 – Price $3.00

people other than the astronauts suffered from two or three episodes of illness during the winter.

Whether or not an individual inclines toward skepticism or apprehension regarding space hazards to man's resistance, all will agree that there are great gaps in our knowledge of this area, and that there is pressing need for additional studies in man.

Before proceeding to a review of the literature, it should be noted that this subject received consideration at an earlier Wood's Hole conference. Dr. J. C. Ross summarized the deliberations, conclusions, and recommendations in a publication of the National Academy of Sciences - National Research Council. This chapter is summarized below.

* * *

Ross, J. C.
Infection.
Chapter 17 in "Physiology in the Space Environment, Vol. II, Respiration." National Academy of Sciences - National Research Council Publication 1485 B, Washington, D. C. 1967. Report of A Conference Conducted By The Space Science Board, NAS-NRC, Woods Hole, Mass., June-July 1966.

Dust particles, due to zero G, will accumulate in the cabin atmosphere, and if a disseminator of pathogens is aboard, high concentrations of infectious particles would be expected. The author cites the common military experience when new recruits are first brought together; there is an increase in acute respiratory diseases until all the members have had, and are immune to, all the infections present in the group.

Current knowledge suggests:

1. Microbial infections may be a problem during prolonged space flight.
2. Altitude, cold, hypoxia, and other stresses increase susceptibility of some animals to infection.
3. Some noxious trace contaminants (O_3, NO_2) are known to increase susceptibility.
4. Studies thus far, up to 56 days in a confined helium-oxygen environment at reduced pressures have given no indication that man's susceptibility to infection is altered.
5. No immunological alterations have been found in those studied before and after actual space flight.
6. No changes in autoflora have thus far been detected.
7. Some effect of weightlessness on the airborne spread of infection can be postulated, but actual studies have not been conducted.

Research is needed on the effects of:

1. Acceleration on susceptibility to aspiration from the mouth and gums.
2. Prolonged exposure to high concentrations of oxygen at less than ground level pressure, for longer periods than 68 days.

In-flight studies are needed:

1. Bacteriological and immunological studies on space crews and cabin atmospheres; effects of space cabin atmosphere and zero-gravity on mucociliary function and resistance to infection.
2. Evaluation of technical aspects of disinfection or biological filtration of cabin air.

General recommendations:

1. To prevent insofar as possible incidence of significant infections in flight:
   a. Selection of crews with similar immunological patterns
   b. Isolation of crews in advance of prolonged space flight, to prevent exposure to new infection and to allow cross immunity to develop.
   c. Determination of microbial content, and development of techniques for maintaining control, in the space vehicle.
2. Develop techniques for handling infections which do occur.
3. Determine effects of respiratory infections on respiratory function.

RADIATION AND INFECTION IN SPACE FLIGHT

Radiation effects on man and other species have been studied extensively over the past 25 years. Radiobiological factors in manned space flight have been exhaustively reviewed by the Space Radiation Study Panel of the Life Sciences Committee, Space Science Board. Their comprehensive report was edited by Langham (1967). The radiation environment in the atmosphere and space is well known and was recently reviewed by Schaefer (1968) in a joint report from the Naval Aerospace Medical Institute and the National Aeronautics and Space Administration.

Sources of Radiation Exposure: Space radiation is derived from three sources consisting of 1) cosmic (galactic) radiation, 2) the Van Allen radiation belts, and 3) radiation from solar flares.

Cosmic radiation is apparently of minor significance, because the observed amounts do not exceed 30 to 50 millirads per day. Van Allen radiation is confined to the radiation belts resulting from the trapping of protons and electrons by the earth's magnetic field. These particles therefore travel in closed trajectories within well defined limits. They may be avoided in flight, or the exposure time may be limited by choosing an appropriate flight path or by adequate shielding. In deep space ventures such belts need to be penetrated only on exit and reentry. However, circular or orbital missions might extend the exposure times to unsuitable length unless the well-recognized precautions are taken to avoid intermittent or continuous operation within a belt.

Solar flares represent the greatest radiation hazard in the space environment, because heavy fluxes of high energy particles are emitted, consisting of protons, alpha particles, and heavy nuclei. Flares occur at random intervals, but most frequently during the active phase of the eleven-year solar cycle. The magnitude of the dosage varies over a wide range, and dangerously large flares are rare.

Hazards of Radiation Exposure: The fundamental damage produced by radiation occurs at the molecular and cellular levels, and is dependent on the dose, on the specific tissue involved, and on the total volume irradiated. The effects are either 1) somatic (early, and late or delayed) or 2) genetic. The early somatic effects following an excessive and massive exposure beyond allowable amounts would produce sudden illness and incapacitation, as characterized by acute irradiation sickness. Such an acute exposure would result in termination of any mission, and would end with death of the subject. Late effects of a lesser but still excessive exposure might allow completion of the mission, but signs and symptoms developing after a delay could produce various secondary effects, including the activation of a normally latent infection. It is with these lesser exposures that an increase in susceptibility to infection can occur from radiation alone, or in combination with other stresses that conceivably could alter the immune mechanisms of the body.

The contribution of infection to radiation mortality has been extensively studied in animals. The combined effects of leucopenia, impaired phagocytosis, inhibition of antibody production, and increased susceptibility to bacterial toxins render the irradiated animal particularly vulnerable to infection from any outside environmental source. He may even suffer bacteremia by invasion from his own intestinal microflora.

Evaluation of Radiation Hazards: All indications from animal data and from flights done to date are that radiation hazards in space flight can be controlled and are of little significance under present day operating conditions. The effects of radiation on the astronauts are no different in space than on earth, both as to total effects and as to susceptibility to infection. Synergistic or additive effects of radiation combined with those of other stresses, such as cabin environment, weightlessness, hypoxia, and hyperoxia, have yet to be studied in detail, though Mieszkuc and Ehrlich (cited in next section) found that 300-500 rads of gamma radiation reduced resistance of mice to K. pneumoniae but not resistance to Staph. aureus.

Dosimetry readings from Apollo flights 7, 8, and 9, indicate that radiation exposure from all sources on the Apollo missions was quite low and that shielding was adequate. Skin radiation was insignificant. Galactic radiation was low, about 10 millirads per day. Personal dosimeter readings on each of the astronauts ranged from 138 to 211 millirems.

Conclusion: In space missions through Apollo 11 it has appeared that radiation effects on susceptibility to infection have been negligible. So long as exposures do not exceed those in past missions, problems are not anticipated. However, prolonged lunar or Mars missions may be attended by hazards, and unless adequate protection or precautions are provided, astronauts may be exposed to doses of radiation which may be damaging. Infection of the exposed individual with normally harmless organisms may be expected as an event in reaction to large doses of radiation.

Arrangement of Literature References on Radiation Effects: The probability that the effects of radiation in space on man's susceptibility to infection are negligible has been deduced from the background provided by a large number of technical publications. These describe experimental results that are of varying degrees of pertinence. Selected publications are classified in the Reference section in categories arranged for consultation by the reader who needs experimental details in the orginal sources.

Classification by Animal Subjects: The significance of irradiation experiments varies with the type of experimental animal subjected to exposure. Experiments on man are directly applicable, but are decreasingly so on primates, larger mammals, murid mammals, and nonmammals, including lower vertebrates and invertebrates. Because of relatively low cost and easy availability of smaller mammals, the quantity of significant results from

these increases in the same sequence. In particular the massive experimentation with laboratory mice is informative, and merits judicious evaluation. Therefore, selected references are noted or described from each of the animal types, and are grouped as above to indicate their relative pertinence to the foregoing interpretation and conclusion.

Radiation Dose and Dose Rate: Chronic exposures to irradiation at low rates have been regarded in this study as an area of particular interest deserving careful evaluation. This is the type of exposure that would be important in the space environment if a subtle or unexpected reduction in infection resistance resulted. Chronic low level radiation exposure is not a commonplace stress in earthbound populations. In prolonged space travel, it might be a hazard unless protective measures were provided. On the other hand, acute exposures at high rates and/or high doses induce well recognized and highly undesirable physiological responses. Such an exposure on a space mission would presumably dictate immediate corrective action or cancellation of the mission, independently of post-exposure dangers of infection. Therefore, we have separated the source reports into the subgroups of Acute or Chronic exposures. Reports of experiments with acute exposures have been examined with emphasis on a search for unusual or unexpected results that might infer enhanced danger of infection even with lower dose rates or long-term chronic exposures,

Selection of Individual References: The preponderance of published information and the general body of clinical experience supports the interpretation we have drawn after extensive examination of the literature. It has seemed unnecessary, however, to list all the references consulted for this review and evaluation, simply as evidence of diligence. We have chosen instead to present in each category a few selected references with brief annotations of part of the significant content. Where there are contradictions, we have attempted to cite both positive and negative reports without commend. Our conclusions in the body of this report are thus not repeated in the annotations.

The annotated references in each category are backed up by additional citations giving only the title of the published article as well as its source. These references are generally confirmatory, although in many cases the titles are useful also to identify the wide variety of infective agents used to challenge the irradiated subjects.

REFERENCES

Summaries on Irradiation vs. Resistance to Infection
Radiation Res., vol. 1, no. 4, Aug. 1954, pp 401-409.

A review of studies concerning increased susceptibility of irradiated animals to experimental infections. The diversity of susceptible animal species tested, as well as the variety of etiologic agents used is described. Increased susceptibility after irradiation is shown not only to many pathogenic bacterial, viral, fungal, rickettsial, helminthic and protozoan agents, but also to ordinarily harmless, common inhabitants of the gastrointestinal tract, such as Escherichia coli and Proteus spp., which became pathogenic and induce fatal infections of the irradiated host. The effects of radiation that may contribute to increased susceptibility are numerous, including such factors as (1) lower peripheral granular leucocyte and lymphocyte counts, (2) suppression of bone marrow and lymphatic tissue elements, (3) inhibition of antibody production, (4) altered activity of the fixed and wandering phagocytic cells, and (5) the impairment of lymphatic blockade and of the screening action of liver and spleen. To determine which of these mechanisms, or what combination of them, may be responsible, it is important to establish quantitative relationships between two factors-the degree to which irradiation affects susceptibility to infection and the post-irradiation time interval required for such susceptibility to reach a maximum.

Shilov, V. M.: The Epidemiological Significance of a Disturbance of Immunity During Infection by Ionizing Radiation. Voenno-Med. Zh., no. 11, 1962, pp 29-33.

Decrease in the resistance of the organism to infection during radiation sickness occurred as a result of a decrease in the phagocytic capability of the leukocytes and the cells of the reticulo-endothelial system and a decrease in the bactericidal properties of blood as a result of inactivation of properdin. The development of autoinfection in radiation sickness cannot be explained by the increase in the permeability of the mucosa, as these phenomena frequently do not correspond in time. Inborn immunity evidently remains essentially unchanged under the effect of radiation sickness. A disruption of artificial immunity was manifested by an almost complete cessation of antibody formation, when antigen was introduced into the organism after irradiation. If radiation affects a process of immunogenesis already begun, almost no decrease in antibody elaboration is observed. Radiation has the following effects on a pre-existant disease: more forms of the disease proceed with greater severity or atypically; chronic processes are exacerbated; and the significance of seriological methods of diagnosis and allergic reactions are lost. Under these conditions, bacteriological diagnosis with the isolation of a pure culture is of basic significance.

Boche, R. D.: Radiation and Susceptibility to Infection. (A Literature Survey) AD-108849, 1954.

Brown, M. H.: Effect of Ionizing Radiation on Immunity. Can. Med. Assoc. J., vol. 87, 1962, pp 1184-1186.

Hale, W. M.; and Stoner, R. D.: Effects of Ionizing Radiation on Immunity. Radiation Res., vol. 1, no. 4, Aug. 1954, pp 459-469.

Kiselev, P. N.; and Buzini, P. A.: The Influence of Chronic Continuous Action of Ionizing Radiation on the Immunity. Med. Radiol., vol. 4, no. 4, 1959, pp 36-44.

Klemparskaya, N. N.: Immunity Reaction in Irradiated Organisms. Med. Radiol., vol. 3, no. 3, 1958, pp 85-90.

Miller, C. P.: The Effect of Irradiation on Natural Resistance to Infection. Ann. N. Y. Acad. Sci., vol. 66, 1956, pp 280-291.

Petrov, R. V.: Exogenous Infections in Radiation Sickness. Usp. Sovrem. Biol., vol. 46, 1958, pp 48-61.

Specific Studies on Radiation Hazards in Space

Conard, R. A.: Hematological Effects of Space Radiation. BNL-10221, 1965.

Available data on the hematological effects of space radiation on man are reviewed. The data indicate that the bone marrow is, under most circumstances, the most critical organ for damage from radiation. The blood forming tissues possibly do not have the regenerative or renewal capacity that the gastrointestinal epithelium has, and will, in most cases, be the limiting factor for survival. Neutrophil and platelet levels will be of primary importance in regard to the fitness and survival of the astronaut from the hematological point of view. Peripheral blood counts, both pre-flight and in-flight, for total white cell count (with neutrophil and lymphocyte levels) offer the best index of prognosis from the point of view of hematopoietic damage. Lymphopenia must be interpreted with caution, since dose distribution patterns and abscopal effects from partial body irradiation may give lower values than indicative of general bone marrow damage. The development of fever, infection, bleeding are signs of severe bone marrow damage. Abortion of a mission is indicated if any accumulated whole body dose of radiation of greater than 150 rads in a 48 hour period occurs; white blood counts drop below 2000 cells per cubic mm and neutrophils below 1000 cells per cubic mm; or if associated fever, infections, or bleeding occur. Very large doses of partial body radiation may be tolerated without lethal depression

of circulating blood cells. Shielding part of the bone marrow may be an important factor in preventing serious hematological depression. It is recommended that serious consideration be given to providing shielding of part of the bone marrow of the astronaut. A lead apron over the pelvic region would shield about 40% of his bone marrow, and he could then withstand considerably larger doses of radiation to the remainder of his body. The dose rate and depth-dose distribution patterns of space radiation are the most important physical considerations in determining total bone marrow damage. High proton flux irradiation associated with solar flares presents the most serious radiation hazard. Based on limited data, the quality of radiation delivered to the bone marrow does not appear to present any special hazards, since the RBE appears to be about 1 or only slightly above for most space radiations that penetrate to the depth of the bone marrow.

Dalrymple, G. V.; and Lindsay, I. R.: Protons and Space Travel: An Introduction. Radiation Res., vol. 28, no. 1, May 1966, pp 365-371.

The radiations found in space can be grouped into four major categories: (1) electromagnetic radiations, (2) electrons, (3) protons, and (4) nuclei of elements with atomic number (Z number) greater than 1. The electrons and electromagnetic radiations have sufficiently low energy (and subsequently low penetration power) that they do not represent a great hazard to the occupant of a space vehicle as long as he remains inside, because the shielding provided by the vehicle walls would be thick enough to absorb these radiations. The protons and heavier nuclei, however, do represent a very real danger because a large number of them have sufficient energy to penetrate the thickest shielding, either available now or planned for years to come. Of these particles, the protons are by far the most hazardous to the space traveler because of the weight of their numbers. Of all the charged particles (excluding electrons) found in space, the protons make up well over 90% of the total. Available data on the origin of protons in space and the reactions of protons in tissue are reviewed. The biological effects of the complex space proton spectrum are discussed.

Dodge, C. H.; and Smith, J. L.: The Effect of Space Flight Factors on Central Nervous System Functions. Surveys of Foreign Scientific and Technical Literature. ATD-66-99; TT-67-60029; AD-642186, Aug. 4, 1966.

The report summarizes 16 articles which concentrate heavily on the isolated and combined effects of acceleration and radiation on mammals. Titles are as follows: effect of radial accelerations on brain temperature; effect of centrifugation on otolith function; effect of vibration on cerebrospinal reflexes; effect of vertical vibration and noise on conditioned reflexes; changes in cerebral bioelectricity and oxygen metabolism; effect of vibration and analyzer exclusion on brain metabolism; cerebral oxygen metabolism, bioelectricity, and conditioned reflex activity during vibration; respiratory changes during vibration; x-ray effect on cerebral venous flow; comparative effect of neutron, proton, and gamma irradiation (300 rad), comparative effect of neutron and gamma irradiation (25 rad); comparative effect of neutron, proton, and gamma irradiation (150 rad); comparative effect of

chronic and acute gamma irradiation and nervous activity; effect of prolonged gamma irradiation on vestibular function; combined effects of vibration and chronic irradiation on vestibular function; combined effects of vibration and ionizing radiation on conditioned reflexes.

Republic Aviation Corp.: Solar Flare Hazard to Earth-Orbiting Vehicles. Final Report. NASA-CR-66202, Apr. 11, 1966.

The object of this study has been to calculate the primary radiation incident on earth-orbiting vehicles during a solar flare. The effects of the earth's geomagnetic field have been taken into account, as well as those of a perturbing field due to the geomagnetic storm associated with a solar flare. Simple earth shadow effects have also been taken into account. Using this primary radiation as source function, dose rates for given orbits are then calculated using a computer routine. Dose rates are computed for typical orbits within a typical vehicle for the solar flares of February 23, 1956 and November 12, 1960.

Schofield, W. M.; Smith, E. C.; and Hill, C. W.: Shielding Problems in Manned Space Vehicles. NASA-CR-68578, Dec. 1962.

The hazards of solar flares to manned space flights are reviewed. It is shown that space radiations incident on material shields produce secondary radiations which may rival or exceed the dose due to primary radiations. Methods of calculating radiation transport through shields are discussed, and the results of sample calculations are presented. An analysis of electron bremsstrahlung produced by electrons in the natural radiation belts shows that this component is small compared to the proton dose for escape missions. However, the electrons resulting from nuclear weapon bursts may possess energies of seven MeV or higher; thus, penetrating electrons may be important for thinly shielded vehicles. It is concluded, therefore, that it would be desireable to develop transport methods for electrons in this energy range.

Langham, W. H., ed.: Radiobiological Factors in Manned Space Flight. National Academy of Sciences, National Research Council, Publ. 1487, 1967.

Schaefer, H. J.: Comparative Evaluation of the Radiation Environment in the Biosphere and in Space, NAMI-1054, Dec. 1968.

Irradiation of Human Subjects

Fiorini, M.; and Zironi, A.: Phenomena of Immunization and Irradiation of the Spleen. Strahlentherapie, vol. 4, 1915, pp 457-465.

Failure to influence the course of lung tuberculosis in man by spleen-irradiation with small doses is reported.

Gremmel, Helmut; and Schulte-Brinkmann, Wolfgang: Existence of a Causal Relationship Between Radiation Therapy and Herpes Zoster. Strahlentherapie, vol. 130, May 1966, pp 57-72.

Twenty-four cases of herpes zoster (0.36%) were observed among 6,655 cancer patients treated during the years 1958 to 1964. With one exception, treatment with ionizing radiation preceeded the eruption of the herpes zoster. A positive causal relationship between radiation therapy and zoster activation could not be found. The zoster incidence rate in irradiated patients was not higher when compared to the non-irradiated patients with malignomas.

Gribova, I. A.: General Nonspecific Immunological Reactivity in Persons Working in Conditions of Chronic Action of Ionizing Radiation. Med. Radiol., vol. 11, no. 9, Sept. 1966, pp 74-78.

Immunological reactivity was studied by an intradermal test with antihuman serum. In persons working in conditions of ionizing radiation in doses not exceeding the maximally permissible levels, no essential changes were observed in the general immunological reactivity.

Lushbaugh, C. C.; Hofstra, R.; Roth, R. E.; and Andrews, G. A.: Radiosensitivity in Man: A Study Based on Therapeutic and Accidental Exposure. Oak Ridge Inst. of Nucl. Studies Med. Div. Res. Rept. Year Ending 31 Dec. 1964., 1964, pp 128-131.

The case histories of 94 patients who had received total-body irradiation in the course of therapy, or as a result of a criticality accident, were encoded and processed to determine the incidence of anorexia, nausea, and vomiting. The patients were divided into five dosage groups for which geometric mean doses of 49.6, 105.2, 300, 370.3 and 540.5 r were determined. The percentage of cases in each group that showed anorexia, nausea, and vomiting are shown. Probability analyses were then done with these data to estimate the total body irradiation dose required to produce the particular response in 50% of the patients. The results are presented in tabulated form. The values are expressed as common logarithm to define the standard deviations of the estimates, and the midline air dose (roentgens), and the absorbed dose (rads) to the gastrointestinal tract. These results appear to indicate that, if it is true that the chance of an astronaut in space receiving 10 rads to the abdomen is less than one in 1000, the chance that radiation-induced severe nausea and vomiting will occur is less than 1:1000,000.

Osgood, H. A.: The treatment of Acute and Chronic Inflammatory Conditions by Fractional Doses of X-ray. Radiology, vol. 32, 1939, pp 311-314.

From clinical experience, fractional doses (20-50 r) of x-radiation given daily are more beneficial than single larger doses. Exacerbations following large doses can be avoided by fractionating the total dose.

Petrov, R. V.: Exogenous Infections in Animals Suffering from Radiation Sickness. Usp. Sovrem. Biol., vol. 46, no. 1, 1958, pp 48-61.

In some infections (herpes in humans), irradiation may cause activation of a latent or chronic infection.

Andrews, G. A.; Sitterson, B. W.; and Nelson, B. M.: Infections in Patients Exposed to Total-Body Irradiation. Oak Ridge Inst. of Nucl. Studies. Med. Div. Res. Rept. Year Ending Dec. 31, 1964. 1964, pp 11-13.

Bond, V. P.: The Role of Infection in Illness Following Exposure to Acute Total-Body Irradiation. Bull. N. Y. Acad. Med., vol. 33, 1957, pp 369-374.

Evans, R. W.: The Antibody Response in Cases of Radiation Lymphopenia and in the Reticuloses. J. Path. Bact. vol. 60, 1948, pp 123-130.

Klemparskaya, N. N.; and Shal'nova, G. A.: Autoflora as an Indicator of Radiative Injury of an Organism. Izdatel'stvo Meditsina, 1966.

Marder, B. B.: Antibody Production in Workers in X-Ray Departments. Med. Radiol. vol. 6, no. 1, Jan. 1961, pp 13-15.

Okunewick, J. P.: The Relationship Between Post-Irradiation Recovery and Equivalent Residual Dose. Med. Radiol., vol. 6, no. 1, Jan. 1961, pp 13-15.

Smith, J. C.: Radiation Pneumonitis. A Review. Am. Rev. Respir. Dis. vol. 87, 1963, pp 647-655.

Irradiation of Primates

Dalrymple, G. V.; Lindsay, I. R.; Ghidoni, J. J.; Hall, J. D.; Mitchell, J. C.; Kundel, H. L. and Morgan, I. L.: Some Effects of 138-Mev Protons on Primates. Radiation Res., vol. 28, no. 2, June 1966, pp. 471-478.

A total of 102 primates (Macaca mulatta) were irradiated with spaced doses of 138-Mev protons ranging from 105 to 1220 rads. Changes indicate an RBE of 1 for 138-Mev protons as compared to 2-Mev x rays. The only findings that were significantly different between these qualities of radiation were clinical. Considerably more pronounced signs of gastro-intestinal injury and hemorrhage were produced by 138-Mev protons as compared to equivalent doses of 2-Mev x rays.

Dalrymple, G. V.; Lindsay, I. R.; Ghidoni, J. J.; Mitchell, J. C. and Morgan, I. L.: Some Effects of 400-Mev Protons on Primates. Radiation Res., vol. 28, no. 2, June 1966, pp. 507-528.

Findings indicate that the effects produced by the protons are virtually identical to those produced by equivalent does of 2-Mev x-rays. The only differences in response were clinical; relatively more intense gastrointestinal and hemorrhagic signs occurred after proton irradiation than after similar doses of x-rays.

Dalrymple, G. V., Lindsay, I. R.; Ghidoni, J. J.; Mitchell, J. C. and Morgan, I. L.: Estimate of the Biological Effects of the Space Proton Environment. Radiation Res., vol. 28, no. 2, June 1966, pp. 548-566.

Small primates (Macaca mulatta) were irradiated with relatively low doses (25 to 400 rads) of either 55- or 250-Mev protons. The biological changes which were demonstrated were directly related to the depth of penetration of the protons as well as to the size of the doses. A summary of the results of the present and prior studies is presented, together with some published physical measurements of the space proton spectrum. Predictions of the biological effects of the protons on man as a space traveler are given. In general, the effects produced by protons are very similar to those produced by supervoltage electromagnetic radiations, when allowance is made for depth-dose distribution.

Dzhikidze, E. K.; and Aksenova, A. S.: The Influence of Low Doses of Ionizing Radiation on the Course of Dysenteric Infection. Med. Radiol. vol. 4, no. 4, April 1959, pp. 44-50.

Monkeys, carriers of dysenteric bacteria for a long period of time, were subjected to x-irradiation in the dose of 5 to 7 r daily (until their death). The animals died in 7 to 14 months, the total dose being 785 to 2060 r. The cause of the animals' death was due to infectious complications: activization of latent dysentery in macaco, and pneumonia and laryngitis is baboons.

Dzhikidze, E. K.; and Aksenova, A. S.: Vaccination of Monkeys Against Gas Gangrene Caused by Cl. perfringens Under Conditions of Extended Irradiation., Zh. Mikrobiol. Epidemiol. Immuniobiol., no. 1, Jan. 1963, pp. 132-137.

The authors studied the effect of irradiation in small doses, repeated over long periods, on the natural resistance and active immunization of 24 monkeys (Macacus rhesus) infected with gas gangrene. Two-to six-year old animals were irradiated with Co^{60} for 18 to 20 months in daily doses of 1.17 - 1.34 r. The integral dose was 519 - 600 r. Conclusions: Small doses of irradiation over long periods do not reduce resistance to Cl. perfringens, but even seem to stimulate it. Immunogenesis is not affected by integral doses of 500 - 580 r, but a slight negative effect becomes evident with 600 r.

Stasilevich, Z. K.: The Course of Acute Intestinal Infections in Monkeys During the Action of Ionizing Radiation., Med. Radiol. vol. 8, no. 4, Apr. 1963, pp. 53-57.

Sublethal x irradiation on monkeys elevated susceptibility to paratyphoid B fever; however, the infectious process was not aggravated. Irradiation of animals with a similar dose aggravated the infectious process in Heidelberg's salmonellosis. In monkeys with colienteritis the above dose did not influence the natural immunity of animals to this disease.

Lindsay, I. R., Dalrymple, G. V.; Ghidoni, J. J.; Mitchell, J. C.; and Morgan, I. L.: Some Effects of 55-Mev Protons on Primates. Radiation Res., vol. 28, no. 2, June 1966, pp. 446-464.

Kundel, H. L.: Effect of High-energy Proton Irradiation on the Cardiovascular System of the Rhesus Monkey. Radiation Res., vol. 28, no. 2, June 1966, pp. 529-537.

Chronic Irradiation of Larger Animals

Clapper, W. E., Sanchez, A.; and Levy, J.: Immune Response to a Secondary Stimulus With Leptospira canicola and Infectious Canine Hepatitis in Beagles Exposed to SR^{90}. LF-29, June 1966. (AEC)

Beagle dogs were immunized with commercially prepared vaccines of Leptospira canicola and infectious canine hepatitis. Half served as controls and half were allowed to inhale aerosolized particles of Sr^{90}, one, two and seven days before booster injections of the antigens. Secondary responses to both antigens were depressed from 40-50 percent of peak titers in control animals. The peak titer was reached for both antigens within 11 days in both control and exposed dogs. Irradiated beagles recovered the ability to respond to another booster injection five months later.

Draper, L. R.: The Hemolysin Response in Rabbits Immunized During Low-level Cobalt-60 Gamma Irradiation. J. Infect. Diseases, vol. 107, 1960, pp. 34-42.

Rabbits were exposed 17 to 147 days to continuous low-level γ-radiation from a central Co^{60} -source at a dose rate of 11 r during 16 hours per day before a single i.v. injection of sheep red cellstromata; within 4 hours after antigen administration, radiation was resumed at the same dose rate and continued for 5 weeks. Induction period and values of peak titers remained unaffected by radiation, whereas peak titers in most cases were reached up to 6 days later in rabbits exposed to a total dose of above 1000 r as compared to nonirradiated controls or animals receiving smaller doses.

Dzhikidze, E. K.; and Aksenova, A. S. The Influence of Repeated Irradiation on Antibody Formation in Rabbits. Med. Radiol., vol. 9, no. 9, Sept. 1964, pp. 72-75.

Rabbits were subject to daily irradiation in a dose of 4 to 5.2 R for 3 to 18 months. No functional disturbances of antibody formation in response to three introductions of paratyphus vaccine in increasing doses were evident. A partial inhibition of immunogenesis was noted during daily irradiation with a dose of 21 R.

Filatov, P. P.; and Gaidova, E. S.: Immunopathology in a Chronic Exposure to ^{65}Zn. Vest. Akad. Med. Nauk U.S.S.R. , vol. 20, no. 9, 1965, pp. 65-70.

$^{65}ZnCl_2$ was administered orally to rabbits daily for 18 months in a daily dose of 10 μc/kg body weight. The data suggest that an autoimmune mechanism plays an important role in the pathogenesis of chronic radiation injury by ^{65}Zn.

Stepanyan, E. D.: Effect of Ionizing Radiation on Certain Immunobiological Functions of the Blood and Reticulo-Endothelial System (RES). Vopr. Radiobiol. Akad. Nauk Arm. S.S.R. Sektor Radiobiol. Sb. Tr., no. 3-4, 1963, pp. 83-94.

Experiments carried out on rabbits indicate that ionizing radiation and bacterial antigen used separately and jointly change the phagocytic capacity of the reticulo-endothelial system (RES) by two stages: at first they depress it for a short period of time and then stimulate it for a period of a longer duration. Simultaneously, antibody production is inhibited in irradiated rabbits but is stimulated in nonirradiated ones. It is also revealed that both phagocytic and antibody production capacities of the RES appear to function independently of each other.

Draper, L. R.: The Effects of Prolonged Irradiation on the Immune Response. In "Effects of Ionizing Radiation on Immune Processes" (C.A. Leone, ed.) Gordon and Breach, 1962, pp. 221-44.

Kiselev, P. N. and Buzini, P. A.: The Influence of Chronic Continuous Action of Ionizing Radiation on Immunity. Med. Radiol., vol. 4, no. 4, Apr. 1959, pp. 36-44.

Lebedeva, G. A.: Lesions of the Gastrointestinal Tract in Chronic Radiation Sickness Caused by Multiple X Irradiation. Arkh. Patol., vol. 24, no. 10, Oct. 1962, pp. 21-26.

Chronic Irradiation of Murid Animals

Birkner, R.; Meyer, R. D.; and Trautmann, J.: Effect of Small X-Ray Doses on Experimental Septicemia Induced by Bacterium Pneumoniae Friedlander. I. Effect of Small Doses Administered After Infection, vol. 103, 1957, pp. 444-455.

Albino mice were given s.c. injections of various dilutions of Klebsiella pneumoniae suspension 18 hours prior to whole body x-radiation (200 kvp; dose rate 18 r/min.). Single doses of 2 and 10 r were repeated seven times in 4 days. Animals irradiated with a total dose of 70 r outlived those irradiated with 14 r and non-irradiated controls. Doses of 10 r, administered 4 and 28 hours post-infection prolonged the survival time of irradiated mice over the survival time of nonirradiated controls by hours. Male mice were more sensitive to infection and to radiation than female animals.

Birkner, R.; Meyer, R. D.; and Trautmann, J.: Effect of Small X-Ray Doses on Experimental Septicemia Induced by Bacterium Pneumoniae Friedlander. II. Effect of Small X-Ray Doses Prior to Subcutaneous Infection, vol. 103, 1957, pp. 551-558.

Albino mice were exposed to daily doses of 2 or 10 r whole-body x-radiation (200 kvp; dose rate 18 r/min.) on five consecutive days prior to s.c. injection of 0.1 ml Klebsiella pneumoniae suspension in various dilutions. Survival time of animals irradiated with a total dose of 50 r was shortened as compared to that of mice irradiated with 10 r and of non-irradiated controls. Single doses of 10 r, delivered 1 to 5 days prior to injection, had no effect on survival time.

Hammond, C. W.; Anderle, S. K.; and Miller, C. P.: Attempts to Increase Resistance of Mice to Bacterial Infection by Prolonged Low Dose γ-Irradiation, vol. 105, 1960, pp. 1-3.

CF-1 female mice 4 weeks of age were exposed 6 days a week from a 0.5 curie cobalt-60 source to doses of 0.5, 1 or 2 r gamma radiation/day. After 4 to 39 weeks exposure they were challenged by intraperitoneal inoculation of graded doses of Pseudomonas aeruginosa. No detectable effect on host resistance to this experimental bacterial infection was demonstrated.

Quilligan, J. J.; Boche, R. D.; Carruthers, E. J.; Axtell, S. L.; and Trivedi, J. C.: Continuous Cobalt-60 Irradiation and Immunity to Influenza Virus. J. Immunol., vol. 90, no. 4, Apr. 1963, pp. 506-511.

Mice were exposed to Co^{60} γ rays at a dose rate of 9, 16, 33, or 106 r/day for total doses up to 2547 r. After 15 days exposure, they were infected with PR8 strain type A influenza virus. Continuous irradiation results in a continued growth of virus particles in lungs of infected animals and results in much higher titers for longer periods of time than in nonirradiated animals. In the dosages utilized, irradiation interferes with primary influenza virus antibody response, but does not interfere with secondary antibody response.

Peterson, O. P.; and Kozlova, I. A.: The Effect of X-Ray Irradiation on the Elaboration of Anti-Influenza Antibodies Following a Single Vaccination of White Rats. Journal; Vopr. Med. Virusol., no. 5, part 1, 1958, pp. 153-156.

The elaboration of anti-influenza antibodies was inhibited and decreased in rats following irradiation with doses of 600 and 400 r, especially if the irradiation was given 2 days before, or 2 days after vaccination. Irradiation applied 6 and 12 days prior to vaccination inhibited immunogenesis to a lesser degree. Irradiation given on the 12th day after vaccination inhibited immunogenesis somewhat. Doses of 25 and 50 r had almost no effect on immunogenesis.

Remezov, P. I.: The Features of the Course of Certain Virus Infections Against a Background of Radiation. Voyenno-meditsinskiy zhurnal, no. 7, 1960, pp. 40-45.

The author studied the course of various infections (lymphocytic choriomeningitis, acute multiple encephalomyletitis, influenza, tick-borne encephalitis, etc) in white mice subjected to a single daily 500, 400, 300, 200, 100, 50 or 10 r dose (or 0.33 r twice weekly) of X-radiation for more than 6 months. A study was also made of the course of virus infection as affected by a combination of unfavorable factors, such as irradiation plus chilling and exhaustion. Ionizing radiation greatly altered the clinical and virological picture of virus infections. Even comparatively, small doses (300, 200, 100 r and less) reduced the mice's resistance to many viruses. Chronic irradiation in such small doses as 10 r reduced resistance to viruses proportional to the total radiation dose. Prolonged irradiation of mice twice weekly in doses of 0.33 r revealed no deviations in the clinical or virological characteristics of the virus infections.

Steward, R. H.; Pribnow, J. F.; and Silverman, M. S.: Effect of Chronic Gamma Radiation on Airborne Infection of Mice With Listeria monocytogenes. Res., vol. 24, no. 1, Jan. 1965, pp. 96-107.

The susceptibility of mice to an airborne infection with Listeria monocytogenes increased after continuous exposure to γ-radiation delivered at 1.0 to 1.5 rads/hour. The increase in susceptibility became greater, the larger the total radiation dose. After sublethal aerosol challenge, bacterial counts on homogenates from the lung, liver and spleen indicated that a more rapid proliferation of the organism occurred in the organs of Co^{60}-irradiated mice. Furthermore, the ultimate disappearance of L. monocytogenes from the lung and spleen of irradiated mice was delayed by 2 to 4 days in comparison to the removal seen in nonirradiated animals.

Vyazikovtseva, O. N.: The Effect of Small Doses of X-Rays Over a Long Period on the Susceptibility and Immunity of Mice to Influenza. Vopr. Med. Virusol., no. 5, part 1, 1958, pp. 145-147.

White mice were irradiated with 10 and 19 r. daily for 15 and for 30 days. They were then infected with influenza virus. The susceptibility to influenza increased by a factor of 57.5 - 10,000, according to the dose and period of irradiation. The mean titer of antibiotics decreased in the irradiated mice.

Berlin, B. S.: Antibody Responses After Injection of Aqueous and Emulsified Influenza Virus Vaccines in Mice Chronically Exposed to Gamma Rays. Res., vol. 18, no. 2, Feb. 1963, pp. 223-230.

Hammond, C. W.; Anderle, S. K.; and Miller, C. P.: Effect of Continuous Gamma Irradiation of Mice on Their Leukocyte Counts and Susceptibility to Bacterial Infection. Res., vol. 11, no. 1, July 1959, pp. 242-252.

Hammond, C. W.; Anderle, S. K.; and Miller, C. P.: Effect of Daily Exposure to 15 r Gamma Radiation on Susceptibility of Mice to Experimental Infection. Proc. Soc. Exptl. Biol. Med., vol. 104, 1960, pp. 261-263.

Miller, C. P.; and Hammond, C. W. Leukocyte Count and Susceptibility to Bacterial Infection as Affected by Continuous Exposure to Low Dose Gamma Irradiation. AF SAM 57-91, 1957.

Silverman, S.; Kornfeld, L.; and Stewart, R. H.: The Susceptibility of Mice to Airborne Infections Following Continuous Exposure to Low Dose Rate γ-Radiation. Annual Progress Report U.S. Naval Radiological Defense Lab. 1965.

Sivertseva, V. N.: Data on the Reproduction of the Influenza Virus in the Organism of Animals Exposed to Chronic Continuous Radiation. Radiobiologiya, vol. 4, no. 4, 1964, pp. 544-547.

Acute Irradiation of Larger Animals

Bond, V. P.; Silverman, M. V.; and Cronkite, E. P.: Pathogenesis and Pathology of Post-Irradiation Infection. Radiation Res., vol. 1, no. 4, Aug. 1954, pp 389-400.

Infection has no major influence on mortality following exposure to lethal or sublethal radiation doses, but may be the cause of death in animals surviving acute irradiation and developing marrow depletion.

Kahn, R. L.; Kim, S. H.; Curtis, A. C.; and Simons, C. S.: X-Irradiation and Toxin Neutralization by Antitoxin. J. Infect. Diseases, vol. 107, pp 325-331.

Rabbits were given a single dose of 1000 r to an area of a hind leg. At different time intervals after radiation, diphtheria antitoxin was injected s.c. in the irradiated area; simultaneously, 25 MLD of diphtheria toxin (three times the lethal dose) was administered s.c. in the other thigh. Antitoxin injected during the first seven days in the irradiated skin afforded better protection than antitoxin injected into nonirradiated skin; antitoxin did not protect when injected 90 days after radiation into the exposed skin. This difference is explained on the basis of a temporary inability of the irradiated skin to localize the injected horse proteins.

Petrov, R. V.; and Sosova, V. F.: Relative Immunological Tolerance Induced by Irradiation. Radiobiologiya, vol. 3, no. 1, Jan.-Feb. 1963, pp 99-103.

Three groups of facts which support the hypothesis that the tolerance induced by irradiation is not absolute but relative. 1) The suppression of antibody formation after injection of an antigen which is observed in animals after irradiation is very variable in extent. 2) The inductive phase before the appearance of antibody may be greatly prolonged after irradiation of the animal, and leads to the erroneous impression that antibody formation has been suppressed, whereas examination at a late stage would reveal that antibody formation is only delayed, and eventually reaches fairly high titres if the animal lives sufficiently long after irradiation. 3) Autoantibodies are formed in irradiated animals in response to autoantigens produced by the effect of radiation upon the body proteins. Irradiation therefore cannot have produced complete immunological tolerance.

Shevtsova, Z. V.: Causes of Reduced Natural Resistance to Live Brucella vaccine in Irradiated Animals. Zh. Mikrobiol. Epidemiol. Immunobiol., no. 4, Apr. 1964, pp 100-105.

The intensity of Brucella multiplication in the various organs of irradiated and non-irradiated animals does not differ and virulence does not increase. The reduced resistance of irradiated animals to Br. abortus 19-Ba is attributed largely to increased Brucella endotoxin sensitivity and related detoxication mechanism disturbance.

Sidwell, R. W.; Thorpe, B. D.; and Gebhardt, L. P.: Studies of Latent Q Fever Infections. I. Effects of Whole-Body X-Irradiation UPon Latently Infected Guinea Pigs, White Mice, and Deer Mice. Am. J. Hyg., vol. 79, Jan. 1964, pp 113-124.

Latent infections of Coxiella burnetii in guinea pigs and mice were studied in attempts to reactivate the infections by x irradiation, a stressor agent which can cause alterations of many physiological processes in infection. Whole-body irradiation in doses slightly less than or greater than the 21-day LD_{50} caused a definite reactivation of C. burnetii in guinea pigs infected 3 months previously. There was no conclusive evidence of reactivation, on the basis of recovery of organisms, in deer mice or white mice similarly treated, although some evidence of reactivation in white mice was indicated by a transmission of C. burnetii to control mice housed as cage mates with the treated animals. Such a transmission was also observed among the treated guinea pigs, but none could be detected in the deer mice or in non-irradiated control animals.

Vancurik, J.: Effect of X-Irradiation on the Course of Experimental Vaccine Anthrax. Folia Microbiol., vol. 9, May 1964, pp 164-172.

The effect of irradiation on vaccine infection in rabbits, using living anthrax vaccine, was studied, in an attempt to determine the specific features of vaccine anthrax in irradiated animals. The vaccine anthrax infection in irradiated animals was identical with the picture of virulent anthrax. The main cause of anthrax sepsis is not increased sensitivity to the toxin, but the high degree of proliferation of the microorganism in the irradiated organism.

Angevine, D. M.; and Tuggle, A.: The Effect of Roentgen Therapy Upon Infections Produced in the Skin of Rabbits With Cultures of Streptococcus Haemolyticus and Staphylococcus Aureus. Am. J. Roentgenol., vol. 46, 1941, pp. 96-103.

Bisgard, J. D.; Hunt, H. B.; Neely, O. A.; and Scott, P.: The Mechanism of Action of Roentgenotheraphy Upon Infection. Ann. Surg., vol. 115, 1942, pp. 996-1006.

Bisgard, J. D.; Hunt, H. B.; Neely, O. A.; and Scott, P.: Experimental Studies of the Mechanism of Action of X-Ray Therapy Upon Infection. Radiology, vol. 39, 1942, pp. 691-696.

Chekatilo, G. A.: Influence of Irradiation of the Host on the Biological Properties of Staphylococcus. Zh. Mikiobiol. Epidemiol. Immunobiol., no. 5, May 1958, pp. 80-82.

Dixon, F. J.; Talmage, D. W.; and Maurer, P. H.: Radiosensitive and Radioresistant Phases in the Antibody Response. J. Immunol., vol. 68, 1952, pp. 693-700.

Kamalyan, L. A.; and Vartevanyan, Zh. Ts.: Efficiency of Prophylactic Activity of Specific Gamma-Globulin in the Case of Vaccine Keratite in Irradiated and Nonirradiated Rabbits. Vopr. Radiobiol. Akad. Nauk. Arm. S.S.R., Sektor Radiobiol. Sb. Tr., no. 3-4, 1963, pp. 53-57.

Kahn, R. L.: Irradiation and Tissue Immunity. II. Response to Injection of Staphylococci in X-Irradiated Skin Areas of Rabbits. J. Infect. Diseases, vol. 110, 1962, pp. 107-113.

Peterson, O. P.; and Kozlova, I. A.: The Effect of X-Ray Irradiation on the Natural Resistance of Rabbits to the Influenza Virus. Vopr. Med. Virusol., part 1, no. 5, pp. 138-141.

Silant'yev, Ye. I.; Ankudinov, V. A.; and Kolesov, S. G.: Anthrax Immunity Upon the Action of Ionizing Radiation on the Organism. Zh. Mikiobiol. Epidemiol. Immunobiol., 1962, no. 11, pp. 121-123.

Snopkova, V. A.: Effect of Ionizing Radiation on the Immunity to Experimental Paratyphoid in Rabbits. Med. Radiol., vol. 3, no. 4, no. 3, 1958, pp. 87-88.

Vulchanov, V. H.; Vassilev, V. N.; Obretenova, K.; and Belokonski, I. Auto-Immunization and Auto-Allerigization in Guinea Pigs Infected With Tuberculosis With Preliminary X-Ray Treatment. Compt. Rend. Acad. Bulgare Sci., vol. 18, 1965, pp. 165-168.

Acute Irradiation of Murid Animals

Klemparskaya, N. N.; and Shal'nova, G. A.: Recovery of Immunogenesis in Irradiated Animals. Recovery from Radiation Injuries, Atomizdat, 1964, pp 89-95.

A dose of 300 r produces disturbances in immunogenesis which become apparent during the first few days after irradiation, when no clinical symptoms are evident; recovery does not take place until about a month later, which is much longer than is required for the clinical symptoms to disappear.

Lavrent'yev, L. N.: Pneumonia in Rats Exposed to Cold Five Months After X-Irradiation. Med. Radiol. vol. 6, no. 8, Aug. 1961, pp 77-78.

Adult rats were exposed to a total dose of 400 r at 180 kv at a dose rate of 53 r/min. Five months after irradiation the animals were subjected for 24 hours to a temperature level of 2 to 4 degrees centigrade and quickly returned to normal temperature. As a result of this exposure, all the irradiated animals died from pneumonia within 9 to 13 days. All control animals survived.

Smith, W.; Alderman, I. M.; Schneider, C.; and Cornfield, J.: Sensitivity of Irradiated Mice to Bacterial Endotoxin. Proc. Soc. Exptl. Biol. Med. vol. 113, 1963, pp 778-781.

Exposure to cobalt-60 gamma radiation and x-radiation, especially in the lethal range, caused a marked increase in sensitivity of mice to S. typhosa endotoxin. This was most pronounced on the third day after irradiation. At that time the endotoxin LD_{50} in mice given 1000 rads was 0.5 μg compared to a control value of 480 μg per 20 g mouse. Shielding the hind legs was without effect on endotoxin LD_{50} (2.3 μg for 850 r, 200 kv x-rays.) Shielding the back, including the adrenals was partially effective (LD_{50}, 55 μg). Treatment with cortisone had an effect comparable to that of shielding the back. Shielding the front of the animal, including practically all of the intestinal tract, was very effective in spite of the fact that the adrenals were irradiated (LD_{50}, 410 μg). Shielding a small portion of the abdomen was also quite effective in reducing endotoxin sensitivity in the irradiated mice (LD_{50}, 165 μg).

Smith, W. W.; Smith, F.; Alderman, I. M.: Effect of Parenteral Injection of Particulate Matter on Resistance of X-Irradiated Mice to Infection. Am. J. Physiol. vol. 182, 1955, pp 400-402.

Mice were x-irradiated with a single dose of 475 r delivered at 200 kv at a dose rate of 55 r/min. Irradiated and control animals were given i.p. or s.c. injections of 40 mg. of particulate Pyrex glass (70μ) several hours after irradiation. Challenge infections were given 3-13 days later by i.v., i.p. or s.c. inoculations. Resistance to Proteus or Pseudomonas challenge was increased 5-12 days after irradiation although granulocyte counts in tail blood

were no higher than in parallel groups not injected with particulate matter. Both intraperitoneal and subcutaneous injections of particulate matter were effective against intraperitoneal, subcutaneous or intravenous challenge. The injection of glass particles increased survival to almost the same extent in mice immunized prior to irradiation and subsequently challenged with a two-fold concentration of Proteus culture as in mice not immunized and challenged with a 1:10 dilution of the culture.

Abdullayev, M. D.; Kazaryan, A. D.; and Sattar-Zade, A. D.: The Course of Focal Staphylococcal Infection in White Rats at Long Intervals After Whole-Body X-Ray Irradiation. Zh. Mikrobiol., Epidemiol. Immunobiol., no. 6, June 1964, pp 107-111.

Akoyev, I. G.; and Lagun, M. A.: Decreased Immunological Resistance as a Manifestation of the Irreversible Component of Radiation Injuries. Med. Radiol. vol. 8, no. 2, Feb., 1963, pp 47-50.

Berlin, B. S.: Sparing Effect of X-Rays for Mice Inoculated Intranasally with Egg-Adapted Influenza Virus, CAM Strain. Proc. Soc. Exptl. Biol. Med.: (in press).

Chukhlovin, B. A.: The Effect of Preliminary Irradiation of the Organism on the Course of Salmonella Infection. Med. Radiol., vol. 4, no. 4, April 1960, p 86.

Finger, H.: The Supression of Lethal Anaphylactic Shock in the Mouse Through Total-Body Radiation. Z. Naturforsch. 1965, vol. 20b, p 81.

Grigor'ev, I. I.: The Susceptibility of Irradiated Animals to Leptospirosis. Med. Radiol. vol. 3, no. 4, July-August 1968, pp 46-50.

Hadler, W. A.; Ziti, L. M.; and Becak, W.: Effect of Ionizing Radiations on the Rate of Evolution of Murine Leprosy. Intern. J. Leprosy, vol. 32, Apr-Jun. 1964, pp 117-126.

Kiselev, P. N.; and Buzini, P. A.: Remote Immunologic Sequelae of the Effect of Ionizing Radiation. Med. Radiol. vol. 9, no. 5, May 1964, pp 50-58.

Kiselev, P. N.; Sivertseva, V. N.; and Karpova, E. V.: Peculiarities in the Course of Infective Processes Associated with the Action of Ionizing Radiation on the Body. Zh. Mikrobiol. Epidemiol. Immunobiol., no. 10, Oct. 1958, pp 21-29.

Kozlova, I. A.: The Susceptibility of Irradiated Rats and Guinea Pigs to Various Strains of Influenza Virus. Vopr. Med. Virusol., no. 5, part 1, 1960, pp 141-144.

Kozlova, I. A.: The Effect of Ionizing Radiation on the Formation of Influenza Antibody in White Rats. Prob. Virolog., 1958, pp 159-162.

Kundin, W. D.; Chien Liu: Harmon, P.; and Rodina, P.: Pathogenesis of Scrub Typhus Infection (Rickettsia Tsutsugamushi) as Studied by Immunofluorescence. J. Immunol., vol. 93, no. 5, Nov. 1964, pp 772-781.

Lawrence, J. H.; and Tennant, R.: The Comparative Effects of Neutrons and X-Rays on the Whole Body. J. Exptl. Med. vol. 66, 1937, pp 667-687.

Tempelis, G. H.; and Lysenko, M. G.: Effect of X-Irradiation on Trypanosoma Lewisi Infection in the Rat. Exptl. Parasitol., vol. 16, Apr. 1965, pp 174-181.

Perkins, E. H.; and Marcus, S.: Effect of Preradiation Immunization on Resistance to Aerosol-Induced Infection in X-Irradiated Mice. J. Immunol., vol. 79, no. 2, August 1957, pp 136-141.

Peterson, O. P.; and Kozlova, I. A.: The Effect of X-Ray Irradiation After Experimental Influenzal Pneumonia Induced in White Rats, Guinea Pigs and Rabbits. Vopr. Med. Virusol., no. 5, part 1, 1958, pp 135-138.

Popova, O. M.; and Berezina, O. N.: The Effect of Preliminary Roentgen Irradiation on the Susceptibility of White Mice to the Ornithosis Virus, upon Infection with an Aerosol of the Virus. Vopr. Virusol., Mar.-Apr. 1964, pp 213-216.

Remezov, P. I.: The influence of General X-Irradiation and Cooling on the Course of Certain Neurotropic Virus Infections in White Mice. Prob. Virol. 1959, pp 315-318.

Sofronov, B. N.: The Effect of Ionizing Radiation on Experimental Pneumonia Caused by Friedländer Bacillus. Med. Radiol., vol. 3, no. 4, July-August 1958, pp 89-90.

Stewart, R. H.; Hodge, F. A.; and Silverman, M. S.: Effects of Continuous Irradiation of Mice on the Immune Response to Live Listeria Monocytogenes.

J. Infect. Diseases, vol. 117, no. 2, 1967, pp 109-115.

Stubbs, R. K.; Bobalik, G.; and Ercoli, N.: Effect of X-Ray Radiation on Trypanosoma Equiperdum in Vivo and in Vitro. J. Infect. Diseases, vol. 102, 1958, pp 35-43.

Varenko, Yu. S.: Changes in the Sensitivity of Irradiated Mice to Endotoxins of Typhoid Fever and Intestinal Bacilli. Radiobiologiya, vol. 4, no. 3, pp 424-425.

Verain, A.; and Verain, A.: Plasmodium Berghei and X-Rays. Compt. Rend. Soc. Biol. vol. 151, 1957, pp 1164-1166.

Wensinck, F.; Van Bekkum, D. W.; and Renaud, H.: The Prevention of Pseudomonas Aeruginosa Infections in Irradiated Mice and Rats. Radiation Res., vol. 7, no. 5, Nov. 1957, pp 491-499.

Yarinsky, A.: The Influence of X-Irradiation Effects on the Immunity of Mice to Infection with Trichinella Spiralis. J. Elisha Mitchell Sci. Soc., vol. 78, May 1962, pp 29-43.

Yarinsky, A.: Mortality of X-Irradiated Mice Infected with Trichinella Spiralis. J. Parasitol., vol. 48, Feb. 1962, pp 156-157.

CHANGES IN ATMOSPHERIC PRESSURE AND COMPOSITION

A pioneering study on the effects of altitude on resistance to infection was that of Berry, Mitchell, and Rubenstein (1955), who reported that acclimatization of mice to a simulated altitude of 20,000 feet led to a greater resistance to infection with the PR8 strain of Influenza A virus than was noted in animals not so acclimatized.

In the years following Berry's first paper in this field, many workers have reported studies with a number of different infectious agents. Mice have been used in nearly all the studies on infection; guinea pigs have been utilized in one experiment. To the date of this review, ten different infectious agents have been used: Sal. typhimurium, Sal. typhi, P. tularensis, P. pseudotuberculosis, K. pneumoniae, Staph. aureus, influenza virus, Venezuelan equine encephalomyelitis virus, mengovirus, and Chlamydial mouse pneumonitis agent. In addition, altitude effects on antibody production in mice, rabbits, and rats have been reported. Altitude effects on interferon production in mice have also been tested.

Among the reports on all these experiments, there have been many which have indicated seemingly harmful effects of altitude or spacecraft atmospheres on resistance to infection or on mechanisms contributing to resistance. By contrast, many of the experiments have indicated either no effect or one which enhances resistance.

Altitude effects on intestinal flora in lower animals have been reported. Similar studies in man have been reported, but under circumstances such that the effects of altitude could not be separated from those of special foods being tested.

Salmonella typhimurium: Berry (1957) published another pioneering classic paper which has been widely quoted in subsequent years. In this experiment the author exposed one group of ten mice to simulated altitude of 20,000 feet for "three to four months," while ten controls were kept at ground level pressure. Following intraperitoneal infection with Sal. typhimurium, both groups were kept at ground level pressure. The mean survival time of the altitude-exposed group was somewhat shorter than that of controls. Although the results met criteria for statistical significance, a reviewer might wish that more than ten animals had been used in each group. Some concern is justified, moreover, as to whether or not altitude (with hypoxia) should be considered the sole stress to which the test animals were subjected. The test animals were brought "down" for feeding and returned to altitude each day, and these daily excursions of pressure may have presented a potential for damage or stress. Noise is another potential stress factor, which according to Jensen and Rasmussen (1963) may have an influence on resistance to infection, and this of course was not known at the time or commented upon. Berry's experiment has never been repeated, using the same altitude, procedures, and infectious agent. Although his conditions were considerably different (pressure corresponding to 37,000 feet, with 100% oxygen, corresponding to ground-level pO_2), Gordon (1966-69) found that exposure to altitude following infection with this organism had no influence on resistance in mice.

Influenza virus: Conflicting inferences may be found in the literature regarding effects of altitude on resistance to infection with this virus. Somewhat along the lines of the early report by Berry, Mitchell, and Rubenstein (1955) cited above, Trapani(1966) compared mice held at 5,280 feet with those held at 14,150 feet before and after infection, and reported longer survival in the 14,150 feet before and after infection, and reported longer survival in the 14,150 foot group. In contrast, though conditions of exposure were different, Ehrlich and Mieskuc (1969) reported opposite effects on the basis of altitude chamber experiments.

Pasteurella tularensis: Again, conflicting inferences are found in the literature, though conditions of exposure to altitude are not as a rule comparable in different reports. Schmidt, et.al. (1967) first used intermittent exposure to altitude, and reported that animals exposed to altitude before infection with this organism showed increased susceptibility, whereas exposure to altitude after infection had no effect. Using continuous exposure to hypobaric conditions, Ball and Schmidt (1968) reported that exposure before infection had no effect on susceptibility, but exposure after infection increased susceptibility. Schmidt (1969) reported that mice infected with P. tularensis and then kept at a simulated altitude of 18,000 feet with oxygen increased to equivalent of ground level tension, showed no differences in mortality or survival time from controls similarly infected but kept at ground level. In the later report, Schmidt (1969) re-examined the influence of intermittent exposure to altitude before and after infection, this time with oxygen tensions above normal. Under these conditions he concluded that such exposure before and/or after infection reduced resistance.

Staphylococcus aureus: Schmidt, Cordaro, and Ball (1967) reported on the effects of altitude on skin lesions produced in mice by this organism. One group of animals was held at a pressure corresponding to 27,000 feet, with 70% oxygen (ground level pO_2) for 14 days, while controls were held at ground level. Animals in both groups were then given a standard dose of organisms, subcutaneously. Half of the altitude group and half the controls were then placed at altitude, and half of each kept at ground level. The median day of healing was noted in each group. The authors concluded that exposure to altitude prior to infection delayed the healing process, and that lesions in the animals previously exposed to altitude were larger. Intraperitoneal infection of mice was reported by Ehrlich and Mieszkuc (1965), using the same organism. They kept mice at a pressure-altitude of 35,000 feet with sea level oxygen for varing periods before challenge. There was no difference in mortality between the altitude and ambient pressure groups. In a further experiment, the same authors tested the effectiveness of Lincomycin in treating staphylococcal infection in altitude-stressed and normal mice. They reported that treatment with 0.5 or 1.0 CD_{50} was less effective in reducing mortality in altitude-stressed mice than in controls. At doses of 3.0 CD_{50} the difference was absent. The authors also reported that duration of exposure to altitude has an influence on therapeutic value. Mice increased mortality if they had been kept at altitude for three or seven days, but not if they had been kept at altitude for 30 days,

Venezuelan equine encephalomyelitis virus: Ehrlich and Miller (1968) placed

guinea pigs at a pressure altitude of 12,000 feet for 7 or 14 days, and then challenged them with an aerosol of VEE virus. The animals were then kept at ground level pressure. Average survival time of test animals were not significantly different from survival time of animals which had been kept at ground level pressure, though the authors felt that there was a "trend toward higher mortality" in the altitude-exposed group.

Mengovirus: Giron, Pindak, and Schmidt (1967) studied the effect of reduced pressure on mengovirus infection in mice. They reported that resistance was reduced if mice were held at altitude, with ground level oxygen, and were then infected and held thereafter at ground level pressure. Resistance was likewise reduced if normal mice were infected and then taken to altitude. A particularly complex and baffling relationship was noted in animals which were held at altitude for 14 days, brought to ground level for infection and held for different periods, and then returned to altitude. Resistance was not reduced if the animals were returned to altitude immediately or if they were held at ground level for 24 hours. Resistance was reduced, however, if the animals were held for a period of one hour at ground level before being returned to altitude. No hypothesis has been advanced which might explain this relationship. In a later publication, Schmidt (1969) reported studies on mice which were held at altitude or ground level, infected intraperitoneally with this agent, and then placed at altitude or ground level. By estimating LD_{50} doses of the virus in each group, the authors concluded that a change in pressure (altitude to ground or vice versa) reduced resistance. In these studies, ground-level pO_2 had been maintained in the altitude chamber. When the experiment was repeated with a hypoxic environment in the altitude chamber, there was no difference among the LD_{50} doses for the several groups, though there was a suggestion of longer survival time among those kept at altitude after infection.

Klebsiella pneumoniae: Ehrlich and Mieszkuc (1962) kept mice at a pressure altitude of 18,000 feet for different periods before challenge with K. pneumoniae aerosol. They reported that animals held at altitude for three days showed increased resistance. Those held at altitude for seven days showed no difference from controls, while those held at altitude for 30 or 90 days prior to challenge showed decreased resistance. Using the same organism but different environmental conditions (pressure altitude of 35,000 feet, 85% oxygen, 10% CO_2, and 5% N), Mieszkuc and Ehrlich (1969) studied effects of holding mice at altitude for different periods before and after challenge. Animals held at altitude for 3, 7, or 30 days prior to challenge showed no difference in mortality from controls. However, animals held at altitude for 14 days prior to challenge showed higher mortality rates, regardless of pressure levels after challenge. Again using the same organism but different conditions (27,000 feet pressure altitude and 100% oxygen), Ehrlich and Mieszkuc 1969) tested the effects of holding mice at altitude for different periods, and then returning them to ground level for different periods before challenge. Those held at ground level for five or seven days showed no difference in mortality from controls, but those held at ground level for only one hour before challenge showed increased mortality. Levels of significance ($P < 0.1$) in some of these groups are not Commonly accepted.

Statolon protection against mengovirus: Schmidt and Pindak (1967) reported that exposure of mice to a space cabin environment did not influence their susceptibility to mengovirus or eliminate the protective effect of statolon against such infection.

Studies on immune responses: Smith, Altland, and Highman (1961) reported that rats immunized with sheep red blood cells and held at an altitude showed higher antibody titers than did controls kept at ground level. Trapani (1966) reported similarly higher titers of antibodies in mice immunized with bovine serum albumin and kept at 10,600 feet actual altitude, by comparison with controls kept at 5,280 feet. Similarly, Tengerdy and Kramer (1967) reported that rabbits held at altitude after immunization with sheep RBC showed higher titers than controls at 20 days, but that the difference was no longer present at 35 days. By contrast, Giron and Schmidt (1966) found no effect of altitude on antibody responses of rabbits immunized with vaccine virus. Trapani (1969) reported that mice immunized with sheep RBC and held at 14,150 feet actual altitude showed fewer plaque-forming (antibody-producing) cells in spleens than did those held at lower altitudes, and that antibody titers were slightly lower in a 14,150 foot groups than in those kept at lower altitude. Coyne and Ackerman (1969), in an exceptionally well-planned series of experiments, tested the effect of reduced pressures (5 and 7.5 psia) with 100% oxygen, on immune responses of mice following injection of killed Brucella abortus antigen. They determined antibody titers and spleen weights, splenic enlargement being indicative of immunological reaction. They noted that animals exposed in "domes" or chambers to reduced pressure and increased oxygen showed impaired immune responses by comparison with room controls. These investigators had taken the unique precaution of having another set of control animals -- a group kept in the domes, but with normal ground level atmospheric composition and pressure. The "dome controls" showed the same impairment of immune responses as did those exposed to simulated spacecraft environments. The authors concluded that factors in the dome environment other than pressure or atmospheric composition had been responsible for the impaired responses. Noise, vibration, change in diurnal cycles, and degree of confinement were mentioned as possible factors which might have influenced immune responses.

Petrov (1965) expressed the conjecture that, in long-term space travelers, deprivation from daily exposure to changing varieties of microbial flora may result in impairment of the body's immunological ability to cope with infection. To what extent man's health depends upon a continuing variety of microbial challenges is not clear, but apprehension seems scarcely warranted.

Studies on flora of intestinal and respiratory tracts: Gall and Riely (1967) and many others cited in the section on Space Foods have reported careful studies on the flora of respiratory and intestinal tracts of subjects confined in altitude chambers and consuming special foods. Cultures of respiratory tracts of these subjects,as might be expected, reflected some exchange of organisms. Thus in studies on respiratory tract flora it is impossible to separate the effects of atmospheric pressure or composition from those of confinement and crowding. In studies on intestinal flora, such as those of Cordaro and others (1966), it has appeared that changes were more likely attributable to the use of experimental foods than to atmospheric composition or pressure.

REFERENCES

Ball, R. J.; and Schmidt, J. P.: Mortality of Altitude-Exposed Mice Infected with Pasteurella tularensis. Appl. Microbiol., vol. 16, no. 10, Oct. 1968, pp. 1451-1453.

200 mice were exposed to 18,000 feet altitude at 20° C. for 14 days and infected with P. tularensis; half were returned to altitude and half were kept at ground level. An additional 200 mice were kept at ground level for 14 days and then infected; half were kept at ground level pressure and half taken to 18,000 feet altitude in a chamber. Two measures of the rapidity of progression of infection were used: (1) the day when 50% of the animals in each cage were dead; these days were averaged, and (2) the number dead in each cage on the eighth day; these numbers were averaged for each group.

The authors concluded that "a significant increase in susceptibility was seen in mice exposed to hypobaric conditions after infection. Hypobaric conditions before infection had no effect on mortality."

Berry, L. J.: Altitude Stress: Its Effect on Tissue Citrate and Salmonellosis in Mice. Proc. Soc. Exp. Biol. Med., vol. 96, 1957, pp. 246-249.

Ten mice were kept at 20,000 feet for "three to four months", being brought to ambient pressure each day for feeding. They were then infected intraperitoneally with 10^5 Sal. typhimurium, and thereafter kept at ground level pressure. Survival times were compared with ten mice similarly infected, which were kept at ground level before and after infection. The mean survival time of the altitude group was 103 $\pm$ 44 hours, that of controls 150 $\pm$ 27 hours.

Berry, L. J.; Mitchell, R. B.; and Rubenstein, D.: Effect of Acclimatization to Altitude on Susceptibility of Mice to Influenza A Virus Infection. Proc. Soc. Exp. Biol. Med., vol. 88, 1955, pp. 543-548.

Mice acclimatized to simulated altitude of approximately 20,000 feet for three weeks are more resistant to induced infection with PR8 strain of influenza A virus than (a) normal control mice, (b) mice similarly exposed to altitude with three weeks of recovery before infection, and (c) mice made anemic by standardized hemorrhage, the latter three groups showing no significant differences in susceptibility.

Altitude acclimatized mice maintained at simulated altitude for the postinfection period are significantly more resistant than those maintained at normal atmospheric pressures.

Cordaro, J. T.: Sellers, W. M.; Ball, R. J.; and Schmidt, J. P.: Study of Man During a 56-Day Exposure to an Oxygen-Helium Atmosphere at 258 mm Hg. X. Enteric Microbial Flora. Aerospace Med., vol. 37, no. 6, June 1966, pp. 594-596.

Stool cultures throughout the study reflected diminished numbers of enterococci;

this change appeared related to the use of the experimental (freeze-dried) diet, as the numbers of enterococci returned upon resumption of the normal diet.

Coyne, R. V.; and Ackerman, G. A.: Effects of Space Cabin Atmosphere on the immune Response. Aerospace Medicine (in press; accepted for publication in 1969).

The authors administered killed Brucella abortus antigen to mice by the intraperitoneal route, and then exposed them, in "domes" or chambers to atmospheres of 100% oxygen at pressures of either 5 psi or 7.5 psi, simulating the atmospheres of U. S. spacecraft. Two groups of mice were used as controls: one group was kept in a room, at ground level pressure and normal atmospheric conditions, while the other was kept in a dome comparable to that used for the test animals, but with normal ground-level atmospheric composition and pressure. Animals were sacrificed at intervals; antibody titers against Br. abortus were determined and spleens were weighed. A 560% increase in spleen weights seen in room controls was taken as an index of immunological reaction, as it was not seen in animals which had not received the antigen.

Animals exposed to 100% oxygen, at either 5 psi or 7.5 psi, showed significantly less splenic enlargement than did room controls. Antibody titers in animals exposed to 100% oxygen at either pressure were lower than those of room controls, though the differences did not meet the authors' criteria for significance.

A very significant finding reported by these investigators is that the "dome controls"-- i.e., animals held in the chamber with normal atmosphere and pressure -- showed the same impairment of spleen response and of antibody titers as did those exposed to reduced pressure and increased oxygen.

The authors concluded that some factors in the domes, other than decreased pressure or increased oxygen content, had impaired the immune response. They suggested that stress due to some aspect of the dome environment, such as noise, vibration, altered diurnal rhythm, or confinement may result in stimulation and release of adrenal cortical steroids. They note that "studies reporting depression of the immune response following various environmental conditions, viz., hypoxia....., have involved some type of atmospheric chamber or enclosure. Such enclosures may produce an environment which is abnormal in respects other than just oxygen concentration and total gas pressure."

Ehrlich, R,; and Mieszkuc, B. J.: Effects of Space Cabin Environment on Resistance to Infection. J. Infect. Diseases, vol. 110, no. 3, June 1962, pp. 278-281.

Mice were kept at 18,000 feet simulated altitude before challenge with K. pneumoniae aerosol. Some were returned to altitude after challenge. Other mice were kept at ground level pressure before challenge; some of these were retained at ground level, and others placed at altitude, following challenge. Measures of resistance were average survival times for respective groups, and the percent mortality in 14 days. Approximately 1,000 mice were used, in 20 groups of 50 each.

The authors concluded that after three days at altitude, resistance increased. This disappeared in seven days, and the resistance was significantly decreased in animals held at altitude for 30 or 90 days prior to challenge. Among mice

held at ambient pressure before challenge exposure to altitude after challenge had no effect.

Ehrlich, R.; and Mieszkuc, B. J.: Resistance to Experimental Bacterial Pneumonia and Influenza Infection in Space Cabin Environments. Aerospace Med., vol 40, no. 2, Feb. 1969, pp. 176-179.

Four experiments are reported:

I. Mice were maintained at 5 psi and 100% O_2 for 5, 7, 14, 21, and 30 days; they were challenged with K. pneumoniae, and returned to altitude for 14 days. There was reduced resistance ($P < 0.1$) in the 7- and 21-day groups, as well as in the 3, 14, and 30-day groups ($P < 0.05$ for the latter).

II. Mice were maintained at 5 psi with 100% O_2 for 7, 15, and 36 days. They were then challenged with influenza virus and returned to altitude for 14 days. There was increased mortality in the test groups, P being <0.01 in the seven-day group, <0.05 in the 15-day group, and < 0.1 in the 36-day group.

III. Mice were maintained at 5 psi with 100% O_2 for 7, 15, and 35 days. They were then held at ground level pressure for one hour, three days, five days, and seven days, and challenged with K. pneumoniae. There was increased mortality ($P < 0.05$) for animals held at altitude for seven days and one hour at ground level, as well as for those held at altitude for 15 and 35 days and one hour at ground level ($P < 0.1$) for the latter groups. There was increased mortality ($P < 0.1$) for all groups held three days at ground level. For the animals held at ground level for five or seven days, there was no difference between test and controls.

IV. Mice were held at 5 psi with 100% O_2 for 7, 15, and 35 days, then at ground level pressure for one hour, one day, three days, five days, and seven days, and then challenged with influenza virus. Increased mortality ($P < 0.05$) persisted for five days in the group at altitude for seven days. Increased mortality ($P < 0.05$) persisted for one day in the group held at altitude for 15 days. There was no increased mortality in the group held at altitude for 36 days.

Ehrlich, R.; and Mieszkuc, B.J.: Lincomycin Treatment of Staphylococcal Infection at High Altitude. Nature, vol. 207, no. 5001, Sept. 4, 1965, p. 1109.

Two experiments were reported:

I. Mice were kept at 35,000 feet (sea level O_2) for 3, 7, 14, and 30 days. They were then challenged with 1, 3, or 100 LD_{50}'s of Staph. aureus. There was no difference in mortality between altitude and ambient pressure groups.

II. Mice were exposed to altitude as above, and then given 100 LD_{50}'s of Staph. aureus. Then, in 30 seconds, all were given Lincomycin at 0.5 CD_{50}, 1 CD_{50}, and 3 CD_{50} (median curative doses).

Treatment with Lincomycin at 0.5 CD_{50} or 1 CD_{50} was less effective in reducing the mortality of the altitude stressed mice than of the control mice. At 3 CD_{50} the difference was absent. The duration of exposure to altitude also affected the therapeutic value. Increased mortality was observed in mice kept at altitude three and seven days. At 14 days it was higher than controls, but at 30 days the mortality was the same.

"For statistical analysis ('t' test), data from ambient and altitude groups were pooled irrespective of the level of antibiotic or duration of exposure. The difference was significant at 5%. Effectiveness was reduced when the host was kept at altitude of 35,000 feet for up to 14 days."

Ehrlich, R.; and Miller, S.: Effect of High Altitude on Resistance to Inhalation VEE Virus Infection. Arch. Environ. Health, vol. 16, no. 4, Apr. 1968, pp. 469-471.

Guinea pigs were placed in a chamber at a pressure altitude of 12,000 feet for 7 or 14 days, then challenged with an aerosol of VEE virus. They were then kept at ambient pressure.

"The mortality was increased for animals exposed to altitude of 12,000 feet. The increased mortality was not significant at the 5% level. However, a trend toward higher mortality was observed in five of seven groups exposed seven days, and 9 of 13 groups exposed 14 days. Comparison of average survival time revealed no significant effect of altitude stress."

Gall, L. S.; and Riely, P. E.: Effect of Diet and Atmosphere on Intestinal and Skin Flora. NASA CR-661, Apr. 1967.

Eight male subjects were confined for 34 days. Two were kept in a control area, and six in a chamber, at 27,000 feet and 100% O_2 for 20 days of the period. Cultures were made of body areas, throats, and stools. There were slight increases in streptococci in throats and buccal areas. In test and control groups, there was a buildup of bacteria, reaching a plateau at midpoint, then remaining constant or declining. There was slightly more of a buildup in the chamber than in the cottage control. Shigella Poly B, Bethesda-Ballerup, and coagulase positive staphylococci were isolated from some subjects. There was apparently no transfer, except one staphylococcus. There was no ill effect.

It is difficult to separate the effects of atmosphere and pressure from those of confinement and crowding. Dimensions of the chamber and control "cottage" were different, as were numbers of persons confined.

Giron, D. J.; Pindak, F. F.; and Schmidt, J. P.: Effect of a Space Cabin Environment on Viral Infection. Aerospace Med., vol. 38, no. 8, Aug. 1967, pp. 832-834.

Increased susceptibility to mengovirus Infection was demonstrated if animals conditioned to 380 mm Hg total pressure (pO_2 = ground level) for 14 days were returned to ground level after infection, or if non-conditioned animals were exposed to altitude after infection. Conditioned animals remaining at altitude after infection were NOT more susceptible than ground controls. However, if conditioned animals were kept at ground level for one hour and then returned to altitude, they were significantly more susceptible.

Giron, D. J.; and Schmidt, J. P.: Viral Antibody Production in Animals Exposed to a Space Cabin Environment. USAF SAM TR-66-82, Sept. 1966.

Rabbits acclimatized for seven days at a cabin altitude of 18,000 feet with

sea level pO_2 were give a series of injections of purified vaccinia virus over a period of five weeks, in the chamber. Control rabbits were kept at ground level and received identical injections from the same virus pool. Antibodies were tested for neutralization titers and distribution in fractions separated by column chromatography. No differences in antibodies between the two groups were noted.

Gordon, F. B.: effects of High and Low Barometric Pressures on Susceptibility and Resistance to Infection. Continuing Series of Quarterly Status Reports, NASA Contract 3C-R-21-010-010. Present reviews included a group with the earliest covering the period July-September 1966, and the latest January-March 1968.

A continuing series of experiments at the Naval Medical Research Institute has compared, in general and in many separate experiments, responses of animals held in three environmental situations: (a) at 3.1 psi and 100% O_2, corresponding to 37,000 feet with sea leveal pO_2, (b) at 95 psig and 2.8% O_2, corresponding to a depth of 213 feet, and (c) ground level. In addition, a number of experiments with altered pO_2 have been reported.

In a 1966 report, NASA CR-82757 it was noted that mice exposed to chlamydial mouse pneumonitis agent following altitude exposure responded similarly to those which had been held at sea level. However, in 1968 (NASA CR 94346), it was stated that an adverse effect was found when parabaric conditions were imposed before aerosol challenge with Chlamydia. Morever, exposure to altitude after challenge was found to have an adverse effect, according to the latter report.

Studies on enteric flora showed Klebsiella species five logs more numerous in the altitude group than in the controls. Aberrant coliforms were found to be present in increased numbers in the altitude group. Enterococci were significantly increased.

This series also includes a report from a round Table at Hotel Taft on 2 May 1967 (NASA CR-84682). Reports from the several participants are covered in individual reports listed elsewhere in this section.

Green, G. M.; and Kass, E. H.: Influence of Bacterial Species on Pulmonary Resistance to Infection in Mice Subjected to Hypoxia, Cold Stress, and Ethanolic Intoxication. Brit. J. Exp. Pathol., vol. 46, no. 3, June 1965, pp. 360-366.

With hypoxia, the clearance of Staphylococcus albus and staphylococcus aureus was inhibited.

Huang, K. Y.; and Gordon, F. B.: Production of Interferon in Mice: Effect of Altered Gaseous Environments. Appl. Microbiol., vol. 16, no. 10, Oct. 1968, pp. 1551-1556.

Newcastle Disease Virus was used as an interferon inducer. Increased levels of interferon were observed in lung tissue when mice were exposed to 11% O_2 in N_2 for three days before and after, or only after, injection of NDV. Serum interferon was unchanged.

Interferon production was depressed in mice kept at 37,000 feet for two weeks; it was not depressed in mice kept at this altitude for four weeks.

Jensen, M. M.; and Rasmussen, A. F.: Stress and Susceptibility to Viral Infection. Sound Stress and Susceptibility to Vesicular Stomatitis Virus. J. Immunol., vol. 90, no. 1, Jan. 1963, pp. 21-23.

Mice exposed to three hours of 123 db noise at 800 cps immediately before or after infection with VSV, and then exposed similarly each day, were more susceptible to VSV than were controls. Similar results were noted if the mice were inoculated after the second period of stress were more resistant than were controls. Stress periods were reduced to 15 minutes. If mice inoculated just before the second period of stress, they were 43% more susceptible than were controls. If inoculated after the second stress, there was an insignificant 9% increase in susceptibility.

Mieszkuc, B. J.; and Ehrlich, R.: Effects of Space Cabin Environmnents on Infection. NASA CR-62065, Oct. 1966.

The environment selected was 5 psi (27,000 feet). 98% O_2, 25° C., and 50% relative humidity. Mortality was increased significantly when mice were challenged with K. pneumonia aerosols after exposure to the space cabin environments for 3, 14, or 30 days. Also when challenged at ground level 24 hours after 30 or 45 days at altitude. However, mortality was not increased if mice were kept at altitude for 14 days, and challenged 24 hours after return to ground level.

Exposure to the space cabin atmosphere before and after exposure to 300 and 500 rads of gamma radiation resulted in a significant increase in mortality. The space cabin environment alone or with radiation had no effect on Staph. aureus infection or its response to treatment.

Mieszkuc, B. J.; and Ehrlich, R.: Effects of Space Cabin Environments on Resistance of Mice to Infection with Klebsiella pneumoniae. USAF-TDR-64-9. Mar. 1964.

The environment selected was 35,000 feet at 85% O_2, 10% CO_2, and 5% N_2. Mice were kept at altitude for 3, 7, 14, and 30 days prior to challenge with K. pneumoniae aerosols. Others were kept at ground level pressure for similar periods. Following challenge, both groups were divided, half being kept at ambient pressure and half at altitude.

Animals held at ambient pressure before challenge and at altitude after challenge showed no significant difference in mortality ratio from controls kept at ambient pressure before and after challenge.

Animals maintained at altitude for 3, 7, or 30 days prior to challenge showed no significant difference in mortality from controls, regardless of whether held at ambient pressure or altitude after challenge. However, animals held at altitude for 14 days prior to challenge showed higher mortality ratios, regardless of whether held at ambient pressure or altitude following challenge.

Petrov, R.: Problems of Space Immunology. Medical Gazette, (Moscow), Nov. 19, 1965, p. 3.

In this newspaper-type report, the author offers conjecture on immunological hazards from "sealing of people in an ampule." Exchange of microflora among occupants of the capsule, shifts in response to space conditions, possible mutation of organisms, possible impairment of immunity and phagocytosis, and deprivation from replenishment of new organisms, all have a potential for impairment of health. Organisms present on other planets may not be recognized by the body as "foreign", and may be able to proliferate in the body without stimulation of defense mechanisms.

Schmidt, J. P.: Resistance to Infectious Diseases Vs. Exposure to Hypobaric Pressure and Hypoxic, Normoxic, or Hyperoxic Atmospheres. Fed. Proc. vol. 28, no. 3, May-June 1969, pp. 1099-1103.

Mice infected intraperitoneally with P. tularensis or P. psudotuberculosis and kept at a simulated altitude of 18,000 feet with 43% oxygen (normoxic) showed no differences in mortality or survival time from controls similarly infected but kept at ground level.

In a study on hypobaric hypoxia (18,000 feet and 20% oxygen), mice were infected intraperitoneally with P. tularensis. Those kept at altitude and hypoxic showed less resistance than did those kept at ground level after infection, as measured by days when 50% were dead and by numbers dead on the 8th day.

In another study, altitude with hyperoxia (18,000 feet and 100% oxygen) was used, exposures being intermittent. Mice infected interperitoneally with P. tularensis and so exposed before and/or after infection showed shorter survival times than did those kept at ground level before and after infection.

In another series of experiments, four groups of mice were given intraperitoneal doses of mengovirus. One group was kept at a simulated altitude of 18,000 feet with 43% oxygen (normoxic) both before and after infection, another at similar altitude before and at ground level after infection, a third at ground level before and at altitude after infection, and the fourth at ground level both before and after infection. The calculated LD_{50} doses of mengovirus were slightly lower in the animals subjected to changes in pressure (altitude to ground or vice versa) than in those kept continuously at altitude or ground level before and after challenge, suggesting that changes in pressure reduced resistance. Similar studies were then carried out using 18,000 feet simulated altitude but with only 20% oxygen (hypoxic environment). Under these conditions of mild hypoxia, there were no differences among the LD50 doses for the four groups, but there was a suggestion of longer survival among those kept at altitude after infection.

A listener to Dr. Schmidt's paper noted that experiments reported here were based on groups of mice kept ten-to-a-cage, and pointed out that in radiation studies, if postirradiated animals are kept one to a cage, results are different from those obtained with two, five or ten to a cage. Dr. Schmidt replied that he had seen no evidence of cross infection, and that since all groups were handled in the same way, there was no reason to question the validity of the data.

Schmidt, J. P.; Cordaro, J. T.; and Ball, R. J.: Effect of Environment on

Staphylococcal Lesions in Mice. Appl. Microbiol., vol. 15, no. 11, Nov. 1967, pp 1465-1467.

197 mice were exposed to pressure corresponding to 27,000 feet, with 70% O_2 (ground level pO_2) for 14 days. CO_2 was absorbed. Temperature was held at 20° C. 192 mice were held at ground level. All were then given subcutaneous injection of 3.5×10^8 colony-forming units of Staphylococcus aureus. Each group was then divided into two, one being held at ground level and the other at altitude. The median day of healing was reported:

a. Ground -- ground 20.8 days
b. Altitude -- altitude 35.3 days
c. Ground -- altitude 20.9 days
d. Altitude -- ground 35.4 days

It was concluded that holding at altitude prior to infection delayed the healing process. Moreover, lesions in the animals previously exposed to altitude were said to be larger.

"Healing" was not defined. Individual lesions were not reported as having been measured.

Schmidt, J. P.; Cordaro, J. T.; Busch, L. F.; and Ball, R. J.: Influence of Intermittent 98% Oxygen at 380mm Hg Pressure on Susceptibility to Tularemia. USAF SAM-TR-67-9, Jan. 1967.

Mice were conditioned by exposure three times weekly for two weeks at 98% oxygen and 380 mm Hg pressure for two to eight hours of exposure. They were then infected intraperitoneally with Pasteurella tularensis and similarly exposed or kept at ground level. The length of exposure did not influence susceptibility. Animals exposed to altitude before infection, regardless of conditions after, showed increased susceptibility. Conditioned animals receiving additional exposure were not more susceptible than those retained at ground level after infection.

Schmidt, J. P.; and Pindak, F. F.: Statolon-Induced Resistance of Mice to Mengovirus. Appl. Microbiol; vol. 15, no.3, May 1967, pp. 654-656.

Mice receiving statolon intraperitoneally were 1,000 times more resistant to intraperitoneal challenge with mengovirus than were untreated controls. Protection was afforded when statolon was administered one day before or one day after intraperitoneal inoculation with the virus. No therapeutic effect was observed when treatment with statolon was delayed for two days or more after infection. Exposure of mice to a simulated space cabin environment did not increase their susceptibility to the lethal effects of mengovirus infection or eliminate the protective effect of statolon.

Smith, F; Altland, P. D.; and Highman, B.: Effect of High Altitude Acclimatization on Formation of Sheep Erythrocyte Hemolysin in Rats. J. Infect. Diseases, vol 108, no.3, June 1961, --. 311-314.

The antibody response of rats to sheep erythrocytes was increased when the animals were exposed to an altitude of 16,000 feet. The same authors reported similar findings in rabbits in the same journal, vol 113, pages 228 232, 1963.

Tengerdy, R. P.; and Kramer, T.: Immune Responses of Rabbits During Short Term Exposure to High Altitude. Nature, vol. 217, Jan. 27, 1968, pp. 367-369.

Rabbits were exposed to a simulated altitude of 20,000 feet, either before or concurrently with immunization with ovotransferrin and/or sheep erythrocytes. One group which received altitude exposure and immunological stimulus concurrently showed significantly higher hemagglutinin titers at 20 days, though the difference was no longer present after 35 days. The anamnestic response was not influenced by altitude.

Trapani, I. L.: Altitude, Temperature, and the Immune Response. Federation Proceedings, vol. 25, July-August 1966, pp. 1254-1263.

A group of test mice were kept at an altitude of 10,600 feet, and controls were kept at Denver (5,280 feet). Both were immunized with bovine serum albumin. Antibody titers were higher in the altitude group.

A group of mice kept at Denver, and another adapted to 14,150 feet were infected intranasally with PR^8 influenza virus. One half of the Denver group was dead in six days; one half of the altitude group was dead in 28 days.

Trapani, I. L.: Environment, Infection, and Immunoglobulin Synthesis. Fed. Proc. vol. 28, no. 3, May-June 1969, pp. 1104-1106.

Mice were acclimatized and kept at three different altitudes: 5,280 feet 10,600 feet, and 14,150 feet. Eighty mice at each altitude were immunized with similar doses of sheep red blood cells. At each altitude, one group of eight mice were sacrificed each day for ten days after injection, for determination of antibody titers and enumeration of plaque-forming (antibody-forming) cells in the spleen. The animals kept at 14,150 feet showed fewer antibody-producing cells in spleens on the fourth day -- the day of maximum response -- than did those kept at lower altitudes.

Circulating antibodies reached a peak in five days in the animals kept at 5,280 feet, in four days in those kept at 14,150 feet, and in six days in those kept at 10,600 feet; antibody titers from animals kept at 14,150 feet were somewhat lower than those of animals kept at 5,280 feet or 10,600 feet. Serum specimans were treated with 2-mercaptoethanol (2-ME), which allows differentiation of large molecular weight immunoglobulins (2-ME sensitive) from those of lower molecular weight. Titers after 2-ME treatment were the same for all altitude groups, suggesting that the superior responses at lower altitudes were attributable to immunoglobulins of high molecular weight.

Zeft, H. J.; Marable, I. W.; Casey, H. W.; and Glenn, W. G.: Effect of High Altitude Hypoxia on Antiheart Antibodies and Experimental Myocarditis. Arch. Pathol, vol. 82, Nov. 1966, pp. 434-442.

Antiheart antibodies were not increased by hypoxia. There was slightly more focal myocarditis seen in the hypoxic animals.

SPACE FOODS

Nutritional adequacy of foods developed for space operations has not been questioned. The possibility that the prolonged use of these special foods might produce a harmful effect through alteration of the intestinal flora has been the subject of considerable study. Gall, Riely, and associates (1969, 1966, 1966, 1966) have reported upon groups of subjects confined in space cabin simulators and using freeze-dried diets. In some reports a shift in types of organisms has been noted. In one of the reports (1966) the shift was said to have resulted in a flora having a reduced capacity for synthesis of certain B-vitamins. In no case, however, was there any clinical evidence of disease or reduced resistance to infection. In one instance a paracolon organism (Bethesda-Ballerup group) of uncertain pathogenicity was isolated from one subject after having previously been isolated from another, with an implication of possible transmission or exchange. Cordaro and colleagues (1966) reported upon an eight-week study of subjects confined in a chamber at 258 mm Hg pressure and an atmosphere of helium-oxygen. Stool cultures showed counts of all organisms which were normal limits throughout, except for enterococci, which diminished during the use of an experimental freeze-dried diet, and returned on resumption of a normal diet.

The conclusion seems warranted that prolonged use of space foods will not have any deleterious effect on resistance to infection.

REFERENCES

Cordaro, J. T.; Sellers, W. M.; Ball, R. J.; and Schmidt, J. P.: Study of Man During a 56-Day Exposure to an Oxygen-Helium Atmosphere at 258 mm Hg. X-- Enteric Microbial Flora. Aerospace Med., vol. 37, no. 6, June 1966, pp. 594-596.

124 stool specimens were examined in the 56 day study. Counts of all organisms were within normal ranges, except for enterococci, which diminished during the use of experimental freeze-dried diet, and returned on the resumption of the normal diet. The change was not of clinical significance.

Gall, L. S.; and Riely, P. E.: Effect of Diet and Atmosphere on Intestinal and Skin Flora Vol. I - Experimental Data. NASA CR-661, 1967.

Eight health subjects were confined for 34 days using dehydrated space rations. In the feces, certain anaerobes started to increase and continued. Shigella Poly B, Bethesda-Ballerup, and a coagulase positive staphylococcus were isolated from one subject, but caused no illness and were not transferred, except that Bethesda-Ballerup was isolated from the feces on one subject after having previously been isolated from feces of another.

Riely, P. E.: Effect of Simulated Space Conditions Including Diet on Microbial Profiles of Twenty Subjects. Paper presented at 37th Annual Meeting, Aerospace Medical Assn. (Las Vegas, Nev.), Apr. 1966.

Twenty subjects were kept in a chamber for four weeks at altitude, consuming space rations. There was some shifting of anaerobic types of microorganisms in the feces, but no symptoms related to these changes.

Riely, P. E.; Beard, D. B.; and Gatts, J. : Effects Real and Relative of a Space-type Diet on the Aerobic and Anaerobic Microflora of Human Feces. Aerospace Med. vol. 37, no. 8, Aug. 1966, pp. 820-824.

Four subjects were confined in an experimental activity facility for a six-week period. Two used a freeze-dried and compressed space type diet; two used a diet of similar foods, either fresh or canned. Subjects exchanged diets midway in the experiment. Aerobic and anaerobic cultures of stools were made throughout. The authors found some differences among their subjects, by contrast with other reports, notably a greater prevalence of Shigella groups B and AD, and of coli types normally considered enteropathogenic. Some organisms were found which were not identified. No consistent differences appeared in the anaerobic character or types of organisms isolated when the diet was shifted from dehydrated to fresh, or vice versa.

Riely, P. E., Geib, D., and Shorenstein, D.: Determination of the Indigenous Microflora of Men in Controlled Environments. NASA-CR-78599, 1966.

The authors refer to statements of Bell, et al. (Textbook of Physiology and Biochemistry, Williams & Wilkins, 1961), to the effect that Vitamin K is synthesized by intestinal flora, and likely also B vitamins; it is likely that bacterial synthesis in the lower alimentary tract is responsible for supplying a substantial portion of man's daily requirement of riboflavin, nicotinic acid, biotin, folic acid, and vitamin K. Fresh and dehydrated diets were used six weeks.

The authors concluded that a change in predominantly anaerobic bacteria in some cases seemingly resulted in a flora which would produce a smaller amount of vitamins. In particular, B_{12} seemed to be significantly reduced in one experiment, as did riboflavin in four experiments, niacin in four, pantothenic acid in three, and folic acid in four.

The reader should recognize that the reductions in vitamin production were not actually measured, in vivo; rather, they were sums of potentials of strains of organisms isolated.

It was recommended that if certain diets cause substantial lowering of B-vitamins produced by bacteria, then fortification of the diet may be necessary.

El-Bisi, H. J.: Microbiological Requirements of Space Food Prototypes. Army Research Inst. of Environmental Medicine, Activities Report, vol. 17, no. 1, 1965, pp 54-61.

Ewing, W. H.: Intestinal Flora. NASA-SP-70, 1964, pp 221-244.

WEIGHTLESSNESS

Two major effects of weightlessness appear to be of possible significance. Berry (1969) commented upon a lack of sinus drainage in the weightless state, and noted that this might delay recovery from upper respiratory infection. Sinusitis, of course, is not necessarily a complication of every respiratory infection. In the case of the in-flight "colds" suffered by the astronauts in Apollo VII, however, complaints of sinus fullness were noted, and recovery was slow.

Loudon (1964) expressed the view that the lack of gravity might prolong the aerial suspension of droplets and droplet nuclei, leading to a buildup of airborne organisms and particles within the spacecraft. The need for in-flight sampling has been recognized by staff members at the Manned Spacecraft Center but weight and space constraints have prevented incorporation of such studies into mission porgrams to date. It is assumed that studies of this kind are among those to be scheduled for the Orbital Workshop, in the Apollo Applications Program.

Conjecture regarding a further effect of weightlessness was expressed by Zhukov-Verezhnikov (1965). The possibility was noted that weightlessness might have had a part in the induction of phage production in E. coli. There is no evidence to support this conjecture.

A possible beneficial influence of weightlessness may be hypothesized with respect to ciliary clearance of particulate material from the lower respiratory tract. In the absence of gravity, it is entirely possible that cilia of the lower respiratory tract may more easily sweep particles upward so that they may be eliminated. Need for in-flight research in this area, and on pulmonary function, was noted by Ross in 1966.

One additional influence of weightlessness may be noted, though it is not likely to be of significance. In the normal environment convection currents are established around body surfaces by warmth from the body. These currents contribute to the dissemination of skin organisms through the environment. In the weightless state, convection currents do not exist. Conceivably dissemination of skin organisms may be reduced, and the buildup of organisms in the environment may be less notable than in the normal gravity field.

REFERENCES

Berry, C. A.: Preliminary Clinical Report of the Medical Aspects of Apollos VII and VIII. Aerospace Med., vol. 40, no. 3, Mar. 1969, pp. 245-254.

With respect to weightlessness and response to infection, the author notes the lack of sinus drainage during the weightless state, a condition assumed to delay recovery from upper respiratory tract infection.

Loudon, R. G.: Airborne Transmission of Infection in Low Gravitational Fields. Paper presented at 35th Annual Meeting, Aerospace Medical Assn. (Miami Beach, Fla.), May 1964.

Under spaceflight conditions, reduction of gravity will prolong the aerial droplets and droplet nuclei. Physical decay of fallout particles will become negligible, and the removal of particles will depend on impact, filtration, or thermal or electrostatic precipitation. Common saprophytes might initiate infections in a closed ecological system. Skin, hair, clothing, food, and the respiratory tract through the atomization of saliva and droplets from the lower part of the respiratory tract, might be sources.

Zhukov-Verezhnikov, N. N.; Rybakov, N. I.; Kozlov, V. A.; Saksonov, P. P.; Dobrov, N. N.; Antipov, V. V.; Podoplelov, I. I.; and Parfenov, G. P.: Results of Microbiological and Cytological Investigations Conducted During the Flights of "Vostok" Type Vehicles. Problems of Space Biology (U.S.S.R.), vol. 4, 1965, pp. 261-269.

The author conjectures that possibly weightlessness has some part in the induction of phage production in *E. coli* K-12.

CONFINEMENT WITH MINIMAL HYGIENE (CHAMBER STUDIES)

Overcrowding has long been recognized as a factor which favors propagation of diseases spread by contact or through the respiratory tract. Military commanders have been instructed for years to provide 120 square feet of floor area per man in barracks, and have been advised to expect serious problems from propagation of respiratory disease outbreaks when this area is not provided. Standards for volume of space, in cubic feet per man, have been less frequently specified, though 120 square feet of floor area in a barracks with an eight foot ceiling would provide nearly 1,000 cubic feet of volume per man. Such spacious accommodations have of course not been feasible in manned spacecraft to date. With a "population density" higher than the ideal, exchange of microflora among occupants of spacecraft should not be unexpected.

This section summarizes the rather considerable work which has been done on the microbiology of skin and respiratory tracts of subjects confined in altitude chambers for varying periods of time. The next section will summarize observations from actual space missions.

In a few studies cited in this section, daily skin care was carried out. In most, however, it was not. The limited hygiene was therefore additive with confinement and close contact. The degree of crowding in altitude chambers did not as a rule match that of actual spacecraft. Periods of observation ranged from 14 days to 60 days.

Studies on skin flora: In those studies in which daily skin care was permitted, there was no buildup of organisms. In a McDonnell Douglas study (1968), full daily sponge baths were permitted, and it was reported that there were no consistent patterns in the qualitative or quantitative changes in the microbiological flora. Cultures were taken from the axillae, perineal regions, and feet of subjects. Moyer, et al. (1966) likewise noted that a daily sponge bath appeared to keep skin microorganisms in check. Lotter, et al. (1969) reported that skin care possible with five wipes per day prevented buildup of organisms.

In those studies in which such daily skin care was not carried out, or where washing was limited to the hands and face, a buildup of skin organisms was observed. Gall and Riely (Feb. 1967) observed increases of skin organisms in the areas tested through the mid-point of a 34-day study. Most organisms were "normal" skin flora (Staphylococci, micrococci, and diphtheroids), and there was no evidence of harm except for small staphylococcal pustules in one individual. Prince (1967) reviewed evidence of buildup of skin organisms during confinement, most notably in skin of the toes and groin. He felt that skin care with three disposable paper wipes, moistened with water, would be adequate for prevention of any ill effect. Riely (1966) commented upon the buildup of skin microorganisms, and noted that the feet became uncomfortable in some subjects, and persons with histories of athlete's foot tended to have recurrence. Borchardt et al. (1968) reported that groins

and axillae were reservoirs for potentially pathogenic Enterobacteriaceae. Kellett, et al. (1967) reported on the wearing of pressure suits for 20 days. One subject showed some flaking of the skin, and another had two small pustules over the coccyx. Otherwise there were no skin problems. In the McDonnell Douglas study, there was some desquamation of the feet, concurrently with a buildup of micrococci. Rack and Loudon (1965) included preliminary scrubbing with hexachlorophene soap on one side of the body before subjects entered the experiment. In one individual, skin lesions developed on the feet, on the side which had not previously been scrubbed with hexachlorophene soap.

Studies on respiratory tract flora: In most chamber studies some exchange of organisms among occupants has been noted. Lotter et al. (1967) noted "minimal exchange of specific phage types of organisms." In studies at the Naval Air Crew Equipment Laboratory (1966), minimal interpersonal transfer was noted, but the authors emphasized the potential for exchange of pathogenic organisms should they be present in an astronaut, and urged elimination of potentially pathogenic organisms from proposed members of a space crew, in advance of the actual mission. Moyer, et al. (1966) noted evidence of transfer of staphylococci among subjects during a 56-day confinement in a chamber. By contrast, in the McDonnell Douglas experiment (1968) Staph. aureus found in the noses of two subjects prior to the experiment was not transferred to others.

Studies on the environment: Gall and Riely (Oct. 1967) noted a buildup of organisms on surfaces in the environment, which was influenced by the degree of crowding in the chamber. The organisms found reflected the hardier types from skin and respiratory tracts of subjects, including staphylococci, streptococci, and diphtheroids. In the Naval Air Crew Equipment Laboratory report (1966), the buildup in the environment was commented upon,but it was stated that no problem was created. Moyer, et al. (1966) reported cultures from air samples during a 56-day study, and indicated that there was no cumulative increase or decrease of aerobic organisms in the atmosphere.

Isolation and the concept of "microbic shock". Luckey (1966) developed a concept similar to that expressed by Petrov (see 1965 reference in section on atmospheric pressure and composition). This is that space travelers, by being deprived of repeated immunological stimuli resulting from contact with great numbers of people, will lose their capacity to cope with the infectious diseases found on earth. He states that "the accumulated deficits may be lethal when astronauts return to this microbe-dominated earth." This concept gains an element of credibility from experience common to isolated communities in the arctic, where a wave of respiratory disease follows the arrival of a winter visitor from the outside. This is not a comparable situation. While the potential for deconditioning of the defense mechanisms is by no means clear, a conjecture opposite to that of Luckey seems more than warranted. Defense mechanisms against many diseases such as diphtheria, measles, mumps, smallpox, and others, are relatively durable even without periodic renewal of contact with the agent. Returning astronauts might indeed suffer from an attack of

influenza, if a new strain of virus were circulating in their home community upon their return. Other respiratory disease agents might pose similar threats. The likelihood of more serious disease, however, would appear extremely remote on the basis of any present experience.

REFERENCES

Borchardt, K. A.; Vogel, J.M.; and Goucher, C.R.: Bacteriological Profile of Test Pilots and Apollo Vehicle During a Simulated 14-Day Lunar Flight. Aerospace Med., vol. 39, no. 2, Feb. 1968, pp. 166-171.

The vehicle was maintained at 97% oxygen, at 3.75-5.00 psi, and 88° - 90° F. Cultures were made on many surfaces in the vehicle, and from throats, groins, axillae, hands, and feet of the subjects. Contamination of the vehicle was minimal except for the urine receptacle. Of the body areas, the groin and axilla were reservoirs for pathogenic Enterobacteriaceae. Other organisms were non-pathogenic.

Gall, L. S.; and Riely, P. E.: Microbial Interactions of Men and Their Environment Inside a Closed System. Contamination Control, vol. 6, no. 9, Sept. 1967, pp. 20-21.

Studies were done on eight young male subjects who were confined for 34 days. Two were in a control area, and six were in a chamber held at 5 psia with 100% O_2 for 20 days and at ambient pressure for the remaining 14 days. Cultures were made of subjects and environment. The types of microorganisms in the environment reflected the hardier types of organisms isolated from the subjects, such as staphylococci, streptococci, and coliform gram-negative rods. In addition, diphtheroids, bacilli, and slender gram-negative rods were found in the environment. The degree of crowding seemed to influence the results of the buildup, both with respect to numbers and types of microorganisms.

Kellett, G. L.; Turaids, T.; and Coburn, K. R.: Full Pressure Suits and Personal Hygiene (in a Report of the Physiological, Psychological, and Bacteriological Aspects of 20 Days in Full Pressure Suits, 20 Days at 27,000 feet on 100% Oxygen, and 34 Days of Confinement). NASA-CR-708, Feb. 1967, pp. 251-254.

In experiments at the Air Crew Equipment Laboratory, pressure suits were worn for 20 days. Subjects washed their hands and faces only. One subject showed some flaking of the skin. Another had two small pustules over the coccygeal area, which cleared after washing with hexachlorophene soap. Otherwise there were no skin or other problems.

Gall, L. S.; and Riely, P. E.: Effect of Diet and Atmosphere on Intestinal and Skin Flora (in a Report of the Physiological, Psychological, and Bacteriological Aspects of 20 Days in Full Pressure Suits, 20 Days at 27,000 Feet on 100% Oxygen, and 34 Days of Confinement). NASA-CR-708, Feb. 1967, pp. 211-236.

Eight healthy subjects were used, six confined in the ACEL chamber and two controls in a "cottage". The chamber program consisted of one week at ambient pressure, one week at altitude without suits, two weeks at altitude with pressure suits, then at ambient pressure with suits. Cultures were made from throats, buccal areas, axillae, groins, eyes, glans penis, as well as from fecal samples.

The total colonies in all areas increased as the experiment progressed, reaching a plateau for most at mid-point, though throat cultures were more variable. Most organisms represented "normal" skin flora, and there was no evidence of harm in 34 days. Staphlococci, micrococci, and diphtheroids were found on the skin; streptococci and a few micrococci in the throat and buccal area; staphlococci, gram-negative rods, and streptococci were found in the environment. 100% oxygen at 5 psia and the wearing of space suits had no effect on the microflora. One individual developed staphylcoccal pustules, but the organisms were not coagulase positive.

Lotter, L. P.; Horstman, B. S.; and Rack, J. V.: Potential Hazard of Staphylococci and Micrococci to Human Subjects in a Life Support Systems Evaluator. USAF Aerospace Medical Research Laboratories Technical Reports No.'s TR-67-18, TR-67-21, TR-67-43, and TR-67-45, 1967.

Subjects were confined for six week periods(two in controlled activity room, four in chamber) with minimal hygiene (five wipes per day; tooth brush was used with water). Cultures were made of representative skin areas. Subjects remained healthy without decrease in resistance to infection, and there was no buildup of any biochemical types. There was minimal exchange of specific phage types of organisms. Confinement under simulated aerospace conditions and minimal personal hygiene showed no unique requirement for special biomedical criteria.

Luckey, T. D.: Potential Microbic Shock in Manned Aerospace Systems, vol. 37, no. 12, Dec. 1966, pp. 1223-1228.

The author anticipates drastic impairment of astronauts' ability to cope with organisms in the earth environment, as a result of deprivation from repeated exposure to these organisms. He obviously had extremely prolonged journeys in mind. He states that anticipated changes include decreased weight of lymph nodes and decreased plasma cells in tissues, decreased weight of liver and intestinal walls, and low white cell count in blood. Chemical changes expected would be soft stools, odor changes reflecting the dominant microorganisms, decreased liver enzymes for detoxication, decreased complexity of metabolic products from intestinal putrefaction, and decreased synthesis of B vitamins and vitamin K. Serum antibody and gamma globulins will decrease. Susceptibility to virus and certain "non-pathogenic" bacteria (i.e., E. coli) may be increased, and intoxication from bacterial endotoxins would decrease. The accumulated deficits may be lethal when astronauts return to this microbe-dominated earth. The problems may be resolved by oral inoculation to maintain or reactivate defense mechanisms.

McDonnell Douglas Astronautics Co.: 60-Day Manned Test of a Regenerative Life Support System with Oxygen and Water Recovery. Part II - Aerospace Medicine and Man-Machine Rest Results. NASA CR-98500, Dec. 1968.

Four healthy males were kept in a closed space cabin simulator at 362 mm Hg total pressure and 160 mm Hg of oxygen. The regenerative system produced oxygen and water. Subjects gave themselves full body sponge baths.

Microbiological studies were carried out on the water, on skin surfaces (axilla, perineum, feet) and noses and throats of subjects. Staph. aureus in the noses of two subjects was not passed to others. There were no consistent patterns in the qualitative or quantitative changes in microbiological flora. Anaerobes decreased after 25 days, and none were found after 30 days until after egress. There was a lack of Pseudomonas, even though this organism was present in the water. There was some mild desquamation of the feet, concurrent with increased micrococci.

Moyer, J. E.; Farrell, D. G.; Lamb, W. L.; and Mitchell, J. L.: Study of Man During a 56-Day Exposure to an Oxygen-Helium Atmosphere at 258 mm Hg Total Pressure. XI Oral, Cutaneous, and Aerosol Bacteriologic Evaluation. Aerospace Med., vol. 37, no. 6, June 1966, pp. 597-600.

Evidence of staphylococcal transfer between subjects was obtained, but the study suggested no buildup of the aerobic microflora of the skin during the experiment. No cumulative increase or decrease in the numbers of aerobic organisms in the atmosphere was noted. The investigators concluded that for esthetic purposes a sponge bath daily is sufficient to keep skin microorganisms in check.

Naval Air Engineering Center, Air Crew Equipment Laboratory: Report of Physiological, Psychological, and Bacteriological Aspects of 20 Day in Full Pressure Suits, 20 Days at 27,000 Feet at 100% Oxygen, and 34 Days of Confinement. NASA CR-65-394, 1966.

Bacteriological studies indicated that although there was a general buildup of microorganisms on the bodies of the subjects and in their respective environments, this posed no special problem. However, a warning note was sounded. The isolation of Shigella Poly B, Bethesda-Ballerup, and a coagulase positive staphylococcus, all potentially pathogenic, would seem to indicate the necessity for eliminating all potentially pathogenic organisms from a proposed space crew. Although there was minimal interpersonal transfer between subjects, overt transfer can occur, and if highly virulent organisms were introduced, the resulting effect could be catastrophic in a manned spacecraft environment.

Prince, A. E.: Personal Hygiene and Sanitation in Aerospace System. Lectures in Aerospace Medicine, 1967, USAF School of Aerospace Med.

The author surveyed a number of experiments in which subjects had been confined for varying periods with minimal hygiene. He noted most marked buildup of organisms at the toes and groin. There were marked variations among individuals, and in the same individual at different times. No ill effects were noted. He recommended skin care with disposable paper wipes, moistened with water, at the rate of three per day per person. He recommended tooth cleansing with a toothbrush and plain water.

Rack, J. F.; and London, S. A.: Microbial Flora of Normal Human Subjects in a Restricted Environment. USAF Aerospace Medical Research Laboratories Technical Report No. TR-66-59, Dec. 1965.

Subjects were confined for six weeks, wearing the MA-10 full pressure suit half the time. Skin flora changes were noted. Preliminary scrubbing with hexachlorophene soap on one side had been carried out. Three pressure-suited subjects showed skin lesions on the feet, on the side not previously scrubbed with hexachlorophene soap.

Riely, P. E.: Effect of Simulated Space Conditions Including Diet on Microbial Profiles of Twenty Subjects. Paper presented at the 37th Annual Meeting, Aerospace Medical Assn. (Las Vegas, Nev.), Apr. 1966.

Subjects were maintained for four weeks at altitude, with minimal hygiene and on space rations (freeze-dried). Cultures were made of throats, body areas, and stools. There was a buildup in skin levels for 23 days. The feet became uncomfortable in some. Persons with past histories of athlete's foot had recurrence.

Baylor Univ.: Comprehensive Biological Protocol for the Lunar Sample Receiving Laboratory. NASA-CR-92209, June 16, 1967.

Coburn, K. R.: Report of the Physiological, Psychological, and Bacteriological Aspects of 20 Days in Full Pressure Suits, 20 Days at 27,000 Feet on 100 Percent Oxygen, and 34 Days of Confinement. NASA-CR-65394, Apr. 1, 1966.

Madri, P. P.: Isolation of Acinetobacter Anitratus (Debord) Brisou and Prevot, From Room Areas and a Human Subject in a Controlled Activity Facility. Aerospace Med., vol. 38, no. 8, Aug. 1967, pp. 799-800.

Marsh, J. T.: Experimental Studies on Response to Viral Infections. Paper presented at Medical Aspects of Stress in the Military Climate Symposium, (Washington, D. C.), Apr. 22-24, 1964.

Mason, E. E.; and Wilson, C.H.: Contaminants from Manned Spacecraft Simulations. NASA-SP-101, 1965.

COMBINED FACTORS (SPACE OPERATIONS)

In actual space operations it is impossible to separate the effects of the many factors which differ from chamber operations on the ground -- weightlessness, confinement, changes in atmospheric pressure and composition, as well as emotional stress factors and possibly fatigue resulting from demanding pre-flight schedules. Nevertheless, studies on man, in actual space missions, give promise of the only valid information which can be obtained on the question of whether or not spaceflight conditions have an influence on resistance to infection. Fortunately, studies have been begun which may be of predictive value. Opportunities exist for approaches which may yield truly meaningful information.

Imaginative approaches to this problem were reported by the Soviet scientists some years ago. Alekseyeva (1965) reported studies on astronauts in their Vostok series, which included lysozyme determinations, studies on phagocytosis, and throat and skin cultures. All were performed before flight, following flight, and some at intervals thereafter. Changes in all parameters were seen, but it was admitted that they were insignificant because they did not reflect any weakening of resistance to infection. Nefedov, et al. (1966) reported exchange of microorganisms among occupants of space vehicles, contamination of the living environment, and "certain shifts" in immunological reactivity, characterized by disruption of the bactericidal activity of the skin cover, reduction in the phagocytic activity of the leukocytes of the blood, and decrease in lysozyme of the saliva. Unfortunately in the Soviet reports there appears to be an inclination to compare results of pre-mission and post-mission studies, and to consider any difference as a significant response to in-flight stress. Long-term studies in the same individuals were not referred to. It would have been desirable to follow each individual's measurements over a long period, to see what variations might have been noted without the stresses of space flight. More meaningful evaluations of changes following flight might then have been made.

Berry, of the staff of the Manned Spacecraft Center published preliminary reports (1967) on studies conducted in connection with Apollo VII and VIII, Berry et al. (1969) later added some preliminary data from Apollo IX. It was notable that communicable diseases figured prominently among the medical problems of the astronauts in these missions, but the presence in Houston and Cape Kennedy areas of a succession of waves of respiratory diseases made transmission to the astronauts almost inescapable. Plans had been made earlier for isolation of crews for quarantine periods before each mission, but the individual astronauts' pre-mission responsibilities had interfered with this effort. Instead, an attempt had been made to maintain an informal and partial restriction of contacts with strangers. Even this proved difficult to enforce. The three cases of in-flight colds should not have been unexpected under these circumstances, and could scarcely have been attributed to the stresses of flight. Recovery, fortunately, was prompt, without jeopardy to the mission. Some concern regarding the outcome is warranted, however, in case one or more of the astronauts had been exposed to an agent of more serious disease. Numerous episodes occurred during that period when extremely debilitating diseases were

seen to spread through groups of people. Had some of the winter's more severe illnesses -- some of which responded poorly to treatment -- occurred in flight, there might indeed have been serious impairment of the team's function.

Some transfer of throat microorganisms during flight was reported by the Manned Spacecraft Center group. In addition, in a number of instances, organisms of uncertain pathogenicity were found in greater numbers after the flight than before. It was reported that "there were changes occuring which allowed some organisms to come to the fore." Actual numbers were not given in the oral report, nor were any long term studies reported. If the changes were significant, it is uncertain whether they resulted from changes in oxygen tension in the hyperoxic atmosphere, humidity, or possible other stresses of the flight. Several of these factors could be evaluated, in humans, in chamber experiments on the ground.

Interesting studies on serum protein functions, lymphocyte responses, and RNA and DNA synthesis have been begun in connection with the Apollo missions. No changes were noted in Apollo VII or VIII. Cellular changes were considered to have been associated with illnesses in flight.

In-flight infections were not a problem in Apollo missions 10 or 11. At the time of neither launch were significant outbreaks of disease in progress on the ground. Moreover, a reasonably effective pre-flight quarantine was maintained prior to Apollo 11. These observations suggest that environmental conditions, of durations so far experienced, do not significantly lower resistance to infection or enhance the relative pathogenicity of organisms carried by crew members.

REFERENCES

Alekseyeva, O. G.: Some Natural Immunity Factors and Cosmonaut Autoflora During the Training Period and Following the Flights of Vostok 1. Vostok 2, Vostok 3, and Vostok 4. Problems of Space Biology (U.S.S.R.), vol. 4, 1965, pp. 290-303.

The following studies were carried out on Vostok crew members before and after their respective flights: (1) Lysozyme content of saliva, (2) Phagocytosis by neutrophils, and impression smears of the buccal mucosa, and (3) Cultures from the pharynx and the skin of the forearm.

LYSOZYME STUDIES: During the pre-launch period, lysozyme increased in first pilots and copilots. Three days before launch Gagarin and Nikolayev showed distinct increases. Only Gagarin showed increase in lysozyme after the flight.

PHAGOCYTOSIS: Levels were stable during launch and pre-launch periods, and normal in most instances, though activated after flight in Gagarin, Titov, and Popovich. Studies on the oral mucosa showed no consistent or significant changes.

CULTURES: Organisms on the skin and in the throat were within normal limits, though in Titov the number of organisms in the throat on the tenth day after landing were 100 times the number three days before launch. Bactericidal property of the skin was said to have been activated in Nikolayev and Popovich during the training period; in Gagarin, during the weeks after flight, but there was some lability 2½ months after the flight.

"These immunological changes were transient and, for practical purposes, insignificant because they did not reflect any weakening of resistance to microbes. The fact that these changes were much less pronounced in Nikolayev and Popovich indicates that cosmonauts can adapt during a three to four day flight. Signs of stimulation do not appear at all, or are compensated by the end of the flight."

Berry, C. A.: Preliminary Clinical Report of the Medical Aspects of Apollo VII and VIII. Aerospace Med., vol. 40, no. 3, Mar. 1969, pp. 245-254.

In Apollo VIII, the commander had an episode of nausea, vomiting, and headache. It was uncertain whether this was a viral gastroenteritis, which had been prevalent prior to launch, or a reaction to seconal.

In Apollo VII, all three had common colds, causing concern for middle ear aeration on descent, since no sinus drainage occurs in the weightless state.

Immunologic studies (a survey of serum protein functions. lymphocyte response, and RNA and DNA synthesis) showed no changes pre- and post-flight.

Some changes occur in bacterial and fungal flora. They vary from individual, but there are transfers from man to man. There is enhancement of the growth of such gram-positive organisms as Staphylococcus aureus and beta streptotocci, and some inhibition of certain groups within the anaerobic flora.

There were some seborrheic lesions of the face and scalp.

Berry, C. A.; Jernigan, C. A.; Rummel, J.; Johnson, R; Fischer, K.; Leach, C; Mack, P,; Mcqueen, J.; Ferguson, J. K.; Barnes, C.: Report on Apollo Manned Space Flights. Aerospace Medical Association Meeting. (Panel Discussion at 40th Annual Meeting (San Francisco, Calif.), May 1969.)

In oral reports by Dr. Berry and members of his staff, findings from Apollo IX were added to those of VII and VIII, a number of which were mentioned in the publication cited above (reference 2). Much of the detailed material from Apollos IX still awaited processing and analysis on the date of the presentation (May 8, 1969). Nevertheless, a number of important observations related to the problem of resistance to infection were presented.

It was noted that Apollo missions VII, VIII, and IX were conducted through the winter season when repeated waves of influenza and other respiratory diseases were in progress in Houston and/or Cape Kennedy. Among the preflight studies in the three missions, herpes simplex virus was found in two persons, but this was of uncertain significance. In flight, there were among the three missions three cases of coryza-like symptoms, and one of aphthous stomatitis. Following there were: One case of gastro-enterities, suspected of being food-borne, one case of rhinitis from which influenza B virus was recovered, and three cases of influenza like syndromes.

Bacteriological studies: In Apollo VII, a streptococcal species was present in the throats of all three after the mission; it had not been present in the throats of any before, though one had had it on his skin. Members of the genera Staphylococcus, Herella, and Aspergillus were more numerous after than before the mission. In Apollo VIII, one astronaut only had a D. pneumoniae both before and after the mission; this was apparently not passed to the other two. Mimae and Herellae were more numerous after the flight. In Apollo IX, staphylococci and streptococci were no problem, though Herellae were cultured after the mission, and there was a buildup of Aspergillus. It was stated that "There were changes occurring which allowed some organisms to come to the fore." The need for in-flight collection and preservation of specimens was acknowledged.

Nefedov, Y. G.; Zaloguyev, S. N.; Shilov, V. M.; and Borshchenko, V. V.: The Problem of the Formation of the Habitational Environment of the Cabin of a Space Ship. Problems of Space Medicine (U.S.S.R.), 1966, p. 286.

Using phage typing and serum typing, an exchange of microorganisms was demonstrated.

Along with bacterial contamination of the living environment, there were certain shifts in the immunological reactivity, characterized by disruption of the bactericidal activity of the skin cover, reduction in the phagocytic activity of the leukocytes of the blood, and decrease in lysozyme of the saliva.

SUMMARY

RADIATION: Experience in manned space missions through Apollo 11 indicated that doses of radiation so far encountered have not been high enough to have any effect on susceptibility to infection. Greatly prolonged lunar or space missions, however, might introduce possible hazards from doses of radiation which, without protection, might adversely affect resistance to infection.

CHANGES IN ATMOSPHERIC PRESSURE AND COMPOSITION: One wishes that information were available which would fill a simple matrix and would show the effects, in man, of reduced pressure and altered oxygen tensions on mechanisms of resistance to infection. Unfortunately no valid scientific information on these effects in man is available. One is without a basis for refuting the concept developed by some during the fall and winter of 1968-69 that "something was happening" to reduce the astronauts' resistance to infection.

The principal body of information relating to these possible effects is based on experiments with lower animals. Even among these reports of animal experiments, not only are there serious gaps in the matrix of desirable information, but there are conflicting reports and a puzzling lack of consistent effects. Evaluation of the literature is made difficult by the fact that each investigator has introduced factors slightly different from those studied by any other, so that no one's results are really comparable with those of anyone else. The confusion is emphasized by reviewing briefly the results of work with different agents.

In studies on infection of mice with influenza virus, two different investigators reported that altitude, with hypoxia, increased resistance, while others reported that it decreased resistance.

In the case of infection with Sal. typhimurium, one investigator reported that reduced pressure, with corresponding reduction in oxygen tension, prior to challenge reduced resistance. Other investigators used normal oxygen tension and exposed the animals to reduced pressure after challenge, and noted no influence on resistance.

In studies with Staph. aureus, one investigator reported that exposure to reduced pressure prior to subcutaneous infection unfavorably influenced the ensuing skin lesions. Another, using the intraperitoneal route for infection, reported that exposure to reduced pressure had no effect on mortality of the mice.

Infection with Venezuelan equine encephalomyelitis was found not to be significantly influenced by prior exposure to reduced pressure, though the investigators felt that there was a "trend toward higher mortality" in the altitude-exposed group.

In experiments with mengovirus, it has been reported that resistance is reduced if animals held at altitude (normoxic) prior to challenge and are

then kept at ground level following challenge, or if those held at ground level prior to challenge are taken to altitude after challenge. Those kept at altitude before and after infection were as resistant as those kept at ground level throughout unless they were held at ground level for one hour before being returned to altitude. The mechanism by which an hour's stay at ground level disturbs the mechanism of resistance awaits explanation.

In experiments on infection with K. pneumonia, and using reduced pressure without augmentation of oxygen (hypoxic environment) investigators reported that exposure to altitude for three days before infection increased resistance, whereas exposure for 30 or 90 days before infection decreased it. When the experiments were carried out with a normoxic environment, exposure to altitude for three, seven, or 30 days before challenge reduced resistance.

In studies on infection with P. tularensis, results have been reported which are equally difficult to explain. Looking first at exposure to altitude with a hypoxic environment, it is reported that intermittent exposure before challenge lowers resistance, whereas intermittent exposure after challenge has no effect. Changing to continuous exposure reverses the phenomenon; i.e., exposure before challenge has no effect, but exposure after challenge lowers resistance. Changing the environment to normoxic produces a change again, in that exposure after challenge has no effect on resistance. With a hyperoxic environment, however, exposure to altitude either before or after challenge reduces resistance.

In studies on immune responses, some investigators have reported an apparent stimulation of antibody production in animals at altitude, others have reported no effect, and still others have reported an impairment of immune responses. In one experiment in which impairment of immune responses was found in animals held at reduced pressure with a hyperoxic environment, the same impairment was found in animals held in a chamber with normal ground level pressure and atmospheric composition. The authors suggest that noise, vibration, darkness/light, or other stresses may have been associated with confinement in the altitude chamber. They express the view that such stresses may perhaps have been present in the experiments of some other investigators.

The finding of impaired immune response by simple placement of animals in a chamber, with normal atmospheric pressure and composition, may indeed explain many of the inconsistencies noted above. It is doubtful that due attention has been given to duplication, in test and control cnimals, of all stresses save those of altered atmospheric pressures and composition.

Regardless of any possible effects in animals, the applicability to man of conclusions based on animal work is uncertain indeed.

SPACE FOODS: There is no evidence to suggest that special foods developed for use in manned space operations have any influence on resistance to infection. A suggestion has been made that shifts in gastrointestinal flora, in response to the use of these special foods, may lead to a reduced potential for endogenous production of B-vitamims. If this occurs, it is not likely to be of clinical significance if dietary vitamim content is maintained.

WEIGHTLESSNESS: In the presence of upper respiratory tract infection complicated by sinusitis, the lack of gravity may be responsible for impairment of sinus drainage. This problem makes doubly important the pre-flight quarantine of astronauts to avoid contraction of respiratory disease, and the provision of appropriate nasal decongestants. A hypothetical hazard relates to the buildup, in spacecraft atmospheres, of organisms discharged from respiratory tracts of the astronauts, since fallout of particles is reduced. The existence or magnitude of this problem can be studied when space and techniques allow in-flight collection of atmospheric samples.

CONFINEMENT WITH MINIMAL HYGIENE: Space vehicles through the Apollo series have subjected the astronauts to a considerable degree of overcrowding, which makes inevitable the exchange of respiratory tract flora, a phenomenon also seen in chamber studies. This prospect again emphasizes the importance of pre-flight quarantine of crew members, to minimize the likelihood of carrying a respiratory disease aboard.

Prolonged chamber studies have emphasized the potential, in the absence of usual opportunities for skin cleansing, for skin disorders, most notably of the feet.

COMBINED FACTORS (ACTUAL SPACE OPERATION): Exchange of respiratory tract flora among crew members has been reported in both U.S. and Russian operations, and "changes which allowed some organisms to come to the fore." The most striking, and to some the most ominous, experience was the development of communicable diseases by astronaut crew members of Apollo 7, 8, 9, in-flight or post-flight. Some workers felt that this experience reflected a probable impairment of resistance by environmental stresses in flight. On the other hand, however, complete pre-flight quarantine was not attained, and waves of respiratory diseases were in progress at Houston and Cape Kennedy. Comparable illness might have been developed by the astronauts at the same time even if they had not participated in the missions. The experience in Apollo 11 was quite different; there were no in-flight or post-flight infections which could have been attributed in any way to environmental conditions or in-flight stresses. Unfortunately, one can not be certain of the factors responsible for this happy outcome. For the first time a reasonably effective pre-flight quarantine of crew members had been maintained. However, in the period preceding the mission there had been no significant outbreaks of respiratory disease in progress at Houston and Cape Kennedy. This by no means detracts from the importance of pre-flight quarantine for future missions. This experience at least suggests that environmental conditions or stresses in flight of durations thus far encountered do not lower resistance to infections with organisms normally present, or enhance their pathogenicity. Further investigation in man, both in astronauts and in altitude chamber subjects, is needed, however, before ill effects of prolonged exposure to spacecraft environment can be ruled out.

ACKNOWLEDGMENTS

Special acknowledgment is in order for the assistance of several persons not among the authors.

Ruth M. Linebaugh, of the Battelle Memorial Institute, was of great assistance in conducting the literature search and preparing the bibliographies.

Dr. Raymond W. Lang, Associate Professor of Medical Microbiology, Ohio State University, gave generously of his time in reviewing references, and offered numerous suggestions which have been included among the Recommendations. He also provided references not revealed by the searches.

Both Dr. Henry G. Cramblett, Chairman, Department of Medical Microbiology, Ohio State University, and Dr. Colin R. MacPherson, Vice Chairman, Department of Pathology, Ohio State University, provided helpful consultation relating to possible avenues for additional research.

NASA-Langley, 1969 — 4 CR-1487